Selective drugs in Dentistry Managements

Metronidazole – Diclofenac Sodium

(Classification, Choices, Pharmacological Consideration, Contra-indications)

A survey study introduced for the scientific committee to have a degree of Bachelor in Dentistry

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Introduction

Today, analgesics and antibiotics are the most prescribed drugs by dentists. Systemic antibiotic administration and pain medication are often used to treat odontogenic infections. Dentists are confronted with odontogenic infections daily and even experienced clinicians and oral and maxillofacial surgeons face this challenge regularly. For example, a German study showed that 9.2% of all patients visited the emergency outpatient unit due to an odontogenic infection. Approximately half of these patients were treated for an abscess and the other half because of inflammatory infiltration. It is common sense that surgical drainage is mandatory to achieve resolution once the abscess has formed. Antibiotic support is only indicated in special clinical situations, e.g., a compromised immune system. The administration of antibiotics should be limited and reduced as much as possible to prevent resistance development. The most effective and tolerable antibiotic should always be used for empirical antibiotic therapy. In recent years the primary use of penicillin or amoxicillin in odontogenic infections is an international standard . postoperative dental pain, nerve root inflammation, or neuropathic pain, and of course the age and morbidity of the patient influence the selection of analgesics. Because of their constrained metabolism process, the dose for children differs significantly from the adults' treatment. Especially for elderly patients, individual risk factors like renal and hepatic diseases and comedications tend to increase and influence the choice of analgesics

In scientific literature, dental prescriptions are often being analyzed either in selected fields like university clinics or regional surveys , or in specialized sectors of health Reliable structured figures concerning the actual number and structure of prescriptions by dentists on a national scale are hardly available. Therefore, this study aims to analyze and summarize the current dental antibiotic and analgesic prescriptions in Germany for the first time, covering a whole decade (2012 – 2021). The development of the prescription of antibiotics and analgesics is analyzed, and groups of medications are compared. We focused on the absolute and relative increase of the most relevant analgesics and antibiotics in dentistry to highlight relevant trends. It also compares dental prescriptions with total antibiotic prescriptions over the investigation period.

Chapter one

Metronidazole

COMMON BRAND(S): FLAGYL, LIKMEZ
GENERIC NAME(S): METRONIDAZOLE

What is metronidazole, and what is it used for?

Metronidazole is an antibiotic effective against anaerobic bacteria and certain parasites. Anaerobic bacteria are single-celled, living organisms that thrive in environments in which there is little oxygen (anaerobic environments). Anaerobic bacteria can cause disease in the abdomen (bacterial peritonitis), liver (liver abscess), and pelvis (abscess of the ovaries and the Fallopian tubes).
Giardia lamblia and ameba are intestinal parasites that can cause abdominal pain and diarrhea in infected individuals. Trichomonas is a vaginal parasite that causes inflammation of the vagina (vaginitis). Metronidazole selectively blocks some of the functions within the bacterial cells and the parasites resulting in their death.

Uses

- Metronidazole is used to treat parasitic infections including Giardia infections of the small intestine, amebic liver abscess, and amebic dysentery (infection of the colon causing bloody diarrhea), bacterial vaginosis, trichomonas vaginal infections, and carriers of trichomonas (both sexual partners) who do not have symptoms of infection.
- Metronidazole is also used alone or in combination with other antibiotics in treating abscesses in the liver, pelvis, abdomen, and brain caused by susceptible anaerobic bacteria.
- Metronidazole is also used in treating infection of the colon caused by a bacterium called C. difficile. Many commonly- used antibiotics can alter the type of bacteria that inhabit the colon. C. difficile is an anaerobic bacterium that can infect the colon when the normal types of bacteria in the colon are inhibited by common antibiotics.

This leads to the inflammation of the colon (pseudomembranous colitis) with severe diarrheaand abdominal pain.)

- Metronidazole also is used in combination with other drugs to treat Helicobacter pylori (H. pylori), which causes stomach or intestinal ulcers.
- Metronidazole topical gel is used for treating acne rosacea.
- Metronidazole vaginal gel is used for treating bacterial vaginosis.

What are the side effects of Metronidazole

Metronidazole is a useful antibiotic and is generally well tolerated with appropriate use.
The most common and minor side effects include:

- Nausea
- Headaches
- Loss of appetite
- A metallic taste
- Rarely a rash
- Abdominal cramps
- Vomiting
- Diarrhea
- Dry mouth
- Dark-colored urine
- Metallic taste in mouth
- Weight loss (anorexia)
- Dizziness
- Constipation
- Furry tongue
- Rash
- Nasal congestion
- Flushing

- Vaginal dryness

Side effects that are uncomfortable, but may become serious include:

- Brain disease
- Fevers
- Mouth sores
- Pain with urination
- Prickling or tingling sensations that may become permanent
- Cystitis
- Pelvic pain or pressure
- Decrease of libido
- Proctitis
- Stomitis
- Glossitis

Serious side effects of metronidazole are rare and the drug should be stopped if these symptoms appear:

- Seizures
- Damage to nerves resulting in numbness and tingling of extremities
- Peripheral neuropathy
- Encephalopathy
- Aseptic meningitis
- Asceptic meningitis
- Colon cancer in people with Crohn's disease

Dosage of metronidazole

- Metronidazole may be taken orally with or without food.
- In the hospital, metronidazole can be administered intravenously to treat serious infections.
- The liver is primarily responsible for eliminating metronidazole from the body, and doses may need to be reduced in patients with liver disease and abnormal liver function.

Various metronidazole regimens are used. Some examples are listedbelow.

- Amebic dysentery: 750 mg orally 3 times daily for 5-10 days
- Amebic liver abscess: 500-750 mg orally three times daily for 5-10 days
- Anaerobic infections: 7.5 mg/kg orally or by injection every 6 hours for 7 to 10 days not to exceed 4 grams daily.
- Bacterial vaginosis: 750 mg (extended release tablets) once daily for 7 days or 500 mg twice daily for 7 days or 2 g single dose or one applicator-full of 0.75% vaginal gel, once or twicedaily for 5 days.
- Clostridium difficile infection: 250-500 mg orally 4 times daily or 500-750 orally 3 times daily
- Giardia: 250 mg orally three times daily for 5 days Helicobacter pylori: 800-1500 mg orally daily for several daysin combination with other drugs.
- Pelvic inflammatory disease (PID): 500 mg orally twice daily for 14 days in combination with other drugs.
- Trichomoniasis: 2 g single dose or 1 g twice
- Rosacea: apply topical gel 0.75-1% once daily

WARNINGS

General

Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided.

Flagyl (metronidazole) has no direct activity against aerobic or facultative anaerobic bacteria. In patients with mixed aerobic- anaerobic infections appropriate concomitant antibiotics active against the aerobic component should be considered.

Known or previously unrecognized moniliasis may present more prominent symptoms after treatment with Flagyl.

Neurologic

Severe neurological disturbances (i.e. convulsive seizures and peripheral neuropathy) have been reported in patients treated with Flagyl. These have been observed very infrequently.

Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

Flagyl should be used with caution in patients with active or chronicsevere peripheral and central nervous system diseases due to the risk of neurological aggravation.

Patients should be advised not to take alcohol or alcohol-containing medicines during Flagyl therapy and for at least one day afterwards because of the possibility of a disulfiram-like (Antabuse effect)reaction.

Hepatic

Flagyl should be used with great caution in patients with a history of hepatic enzyme increase or liver injury associated with previous administration of metronidazole (see ADVERSE REACTIONS section).

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, with very rapid onset after treatment initiation, in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, Flagyl should therefore only be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking Flagyl.

PRECAUTIONS

General

Where there is clinical evidence of a trichomonal infection in the sexual partner, he should be treated concomitantly to avoid reinfection. A rare case of reversible but profound neurological deterioration hasbeen reported following a single oral dose of Flagyl (metronidazole); it is therefore advisable that a patient taking Flagyl for the first time not be left unattended for a period of two hours. The appearance of abnormal neurologic signs demands prompt discontinuation of Flagyl therapy and, when severe, immediate medical attention. Activated charcoal may be administered to aid in the removal of unabsorbed drug, if no more than two or three hours have elapsed since administration of the drug.

If for compelling reasons, Flagyl must be administered longer than the usually recommended duration, it is recommended that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, convulsiveseizures).

Treatment with Flagyl should be discontinued if ataxia or any other symptom of central nervous system (CNS) involvement occurs.

Patients with severe hepatic disease (including hepatic encephalopathy) metabolize metronidazole slowly with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses of Flagyl below those usually recommended should be administered and with caution.

Treatment with Flagyl should be discontinued should pancreatitis occur once other causes of this disease are excluded.

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administeringmetronidazole injection to patients receiving corticosteroids or to those predisposed to edema.

Patients should be warned that Flagyl may darken urine. This is probably due to a metabolite of metronidazole and seems to have no clinical significance .

Hematologic

Transient eosinophilia and leukopenia have been observed during treatment with Flagyl. Haematological tests, especially regular total and differential leukocyte counts are advised if administration for more than 10 days or a second course of therapy is considered to be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However similar studies in the hamster have given negative results. Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro aswell as in rodent in vivo, there was inadequate evidence of mutagenic effect of metronidazole.

Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reportedstudies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during everyfourth week only).

At very high dose levels (approximately 1500 mg/m2 which is approximately 3 times the most frequently recommended human dose for a 50 kg adult based on mg/m2), there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas aswell as pulmonary neoplasms associated with lifetime feeding of thedrug. All these effects are statistically significant.

Several long-term oral dosing studies in the rat have been completed. There were statistically significant increases in the

incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

The use of Flagyl for longer treatment than usually required should be carefully weighed since it has been shown to be carcinogenic in mice and rats.

Fertility

studies have been performed in mice at doses up to six times the maximum recommended human oral dose (based on mg/ m2) and have revealed no evidence of impaired fertility.

Pregnancy

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Although Flagyl has been given to pregnant women without apparent complication, its effects on human fetal organogenesis are not known; it is advisable that administration of Flagyl be avoided in pregnant patients and be withheld during the first trimester of pregnancy. In serious anaerobic infections, if the administration of Flagyl to pregnant patients is considered to be necessary, its use requires that the potential benefits to the mother beweighed against the possible risks to the fetus.

Nursing Mothers

Metronidazole is secreted in breast milk in concentrations similar to those found in plasma. Administration of Flagyl should be avoided in the nursing mother.

Children

Clinical experience in children is very limited. The monitoring of this group of patients is particularly important.

DRUG INTERACTIONS

Alcohol: Patients taking Flagyl should be warned against consuming alcoholic beverages and drugs containing alcohol during therapy andfor at least one day afterwards, because of the possibility of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia). This reaction appears to be due to the inhibition of the oxidation of acetaldehyde, the primary metabolite of alcohol.

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Cyclosporin: risk of elevation of cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Disulfiram: Administration of disulfiram and Flagyl has been associated with acute psychoses and confusion in some patients; therefore, these drugs should not be used concomitantly.

5-Fluorouracil: Flagyl has been reported to reduce the clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.

Lithium: Concomitant use of lithium and Flagyl may result in lithium intoxication due to decreased renal clearance of lithium. Persistent renal damage may develop. When Flagyl must be administered to patients on lithium therapy, it may be prudent to consider tapering or discontinuing lithium temporarily when feasible. Otherwise frequent monitoring of lithium, creatinine and electrolyte levels and urine osmolality should be done.

Oral anticoagulant therapy (Warfarin type): Metronidazole has been reported to potentiate the anticoagulant effect of warfarin resulting in a prolongation of prothrombin time and increased hemorrhagic risk caused by decreased hepatic catabolism. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy. In case of coadministration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with Flagyl.

Phenytoin or Phenobarbital: In single dose studies, metronidazole injection did not interfere with the biotransformation of diazepam, antipyrine or phenytoin in man. However, patients maintained on phenytoin were found to have toxic blood levels after oral metronidazole administration. Phenytoin concentration returned to therapeutic blood level after discontinuance of metronidazole.
The metabolism of metronidazole has been reported to be increased by concurrent administration of phenobarbital or phenytoin.
Vecuronium: A slight potentiation of the neuromuscular blocking activity of vecuronium has been reported in patients administered metronidazole at a dose of 15 mg/kg.

Risk

ADVERSE REACTIONS
Blood and lymphatic system disorders: transient eosinophilia, neutropenia, very rare cases of agranulocytosis and thrombocytopenia have been reported. Cardiac disorders: palpitation and chest pain.
Eye disorders: transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision. Optic neuropathy/neuritis has been reported.
Ear and labyrinth disorders:
hearing impaired/hearing loss (including hypoacusis, deafness, deafness neurosensory) tinnitus
Gastrointestinal disorders: diarrhea, nausea, vomiting, epigastric distress, epigastric pain, dyspepsia, constipation, coated tongue, tongue discoloration/furry tongue (e.g. due to fungal overgrowth), dry mouth, taste disorders including metallic taste, oral mucositis. Reversible cases of pancreatitis have been reported infrequently.
General disorders and administration site conditions: Thrombophlebitis has occurred with I.V. administration. Fever has been reported.
Hepatobiliary disorders: increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and

hepatocellular liver injury, sometimes with jaundice have been reported.
Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.
Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, in patients with Cockayne syndrome have beenreported with products containing metronidazole.
Immune system disorders: angioedema, anaphylactic shock. Infections and infestations: rare cases of pseudomembranous colitishave been reported.
Metabolism and nutrition disorders: An antithyroid effect has been reported by some investigators but three different clinical studies failed to confirm this. Anorexia has been reported.
Nervous system disorders: convulsive seizures, peripheral sensory neuropathy, transient ataxia, dizziness, drowsiness, insomnia, headache, aseptic meningitis.

What preparations of metronidazole areavailable?

- Tablets: 250 and 500 mg.
- Tablets, extended release: 750 mg.
- Capsule: 375 mg.
- Cream: 0.75% and 1%.
- Lotion: 0.75%.
- Gel: 0.75% and 1%.
- Injection: 5 mg/ml

Metronidazole for Treatment of Non- periodontal Dental Decay

Besides periodontal dental diseases, Metronidazole can treat other dental issues.

1. Indications- Dentists can prescribe Metronidazole for dental abscesses, ANUG, pericoronitis, and endodontic infections. Metronidazole can treat the germs causing these infections, which result in severe pain, swelling, and discomfort.

2. Anaerobic Bacteria- Metronidazole works well against tooth decay-causing anaerobic bacteria. It destroys bacterial DNA, haltinggrowth and multiplication.

3. Combination Therapy- Metronidazole is often taken with different antibiotics to cover various aerobic and anaerobic bacteria. This combination therapy provides comprehensive treatment.

4. Dosage and Duration- Metronidazole dosage and duration depend on the infection, severity, and patient history. To find the best treatment, dentists may perform culturing or sensitivity tests.

Remember that Metronidazole isn't a first-line tooth disease treatment. Dentists will thoroughly evaluate the illness before prescribing Metronidazole or other antibiotics, run any necessary tests, and review the patient's medical history.

Chapter five

Diclofenac Sodium

Voltarine

Introduction

Brand names: voltaren,Voltarol, Dicloflex, Diclomax, Econac, Fenactol, Motifene

Introduction :

Effective management of endodontic pain represents a continuing challenge. Many of the dental professionals are facing significant problems associated with postendodontic pain. Hence, the postendodontic pain has to be prevented at its primary stage without waiting for its occurrence. This trial was carried out to evaluate the use of a preoperative, single oral dose of diclofenac sodium for the prevention and control of postendodontic pain.

Postendodontic pain was substantially reduced by preoperative administration of single oral dose of diclofenac sodium. It is thus possible to conclude that these favorable results might help to prevent postendodontic pain, especially in patients with a low pain threshold.

Endodontic posttreatment pain continues to be a significant problem facing the dental profession.[1] Among patients presenting with preoperative pain, it has been reported that up to 80% of this population continue to report pain after endodontic treatment, with pain levels ranging from mild to severe.[2,3] The possible causes for endodontic inter-appointment pain are related to endodontic instrumentation, irritating irrigants, intracanal medications, periapical contamination, and temporary restorations in hyperocclusion. Irritation of periradicular tissues during root canal therapy causes an acute inflammatory reaction, potentially leading to pain and/or swelling.[3]

Certain factors may influence the progression of postoperative pain, such as a history of preoperative pain and the need for re-treatment.[4] Many chemical mediators have been associated with this inflammatory process. Prostaglandins increase vascular permeability, elevate chemotactic activity, induce fever, and increase sensitivity of pain receptors to other active inflammatory mediators.[2,3]

A variety of approaches have been recommended for the management of interappointment pain. These include occlusal reduction, intracanal medication, prescription of analgesics, and the use of steroidal and nonsteroidal anti-inflammatory agents.[2,3,4] The potential for these anti-inflammatory drugs to

directly or indirectly prevent pain at the site of tissue injury is evidenced by the suppression of the release of inflammatory mediators.[4]

A preoperative single oral dose of anti-inflammatory drugs can modulate release of inflammatory mediators and reduce the occurrence of side effects compared with repeated doses during the postoperative period.[3] Few studies have evaluated the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) with regard to prevention and control of postendodontic pain after root canal instrumentation. Thus, the purpose of the present trial was to evaluate the effect of diclofenac sodium (100 mg) administered as a single, preoperative oral dose for the prevention and control of postendodontic pain.

In a systematic review by Nagendrababu and Guttman in 2017, it was reported that PEP was significantly higher in patients presenting with pain before the commencement of treatment (4). There are various methods to reduce the incidence of PEP, such as the use of an analgesic pre-operatively as well as post-operatively, crown down method of instrumentation, adequate disinfection through irrigation, and relieving of occlusion (4). Among these, the use of oral premedication has been supported by various randomised clinical trials and systematic reviews (4, 5). Oral non-steroidal anti-inflammatory drugs are most frequently prescribed for management of endodontic pain (6). Various comparative studies have reported Oral diclofenac to have a high efficacy in reducing PEP following root canal treatment (7, 8). However, the oral route leads to first-pass metabolism, decreasing its bioavailability and adversely affecting the gastrointestinal system (9). An alternative route of drug administration to circumvent these problems is the use of transdermal patches. In dentistry, several randomised clinical trials have reported a reduction in post-operative pain with the use of transdermal patches in cases of extraction (10), periodontal flap surgery (11), orthognathic surgery (12), and root canal treatment (13, 14).

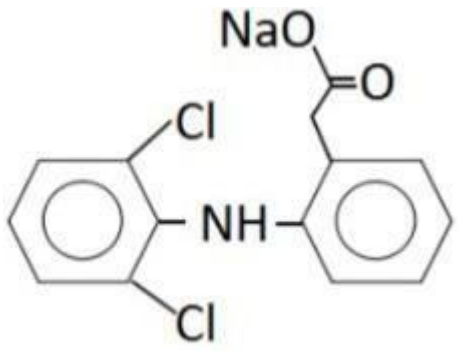
In Endodontics, Mangal et al. in 2020 (13) and Dhanapal et al. in 2016 (14) reported a significant decrease in PEP with oral and transdermal administration of diclofenac with no significant difference between the groups following single visit root canal treatment (SVRCT). In the study by Mangal et al., medication was given post-operatively, and only premolars with single roots were included, whereas, in Dhanapal et al.'s (13, 14) study, the tooth type was not mentioned. In both trials, the sample size was small, which may have caused the validity of the findings of these studies to be considered low. Moreover, none of the studies measured the impact of premedication on PEP and OHRQOL. Hence, this study aimed to evaluate the effect of pretreatment diclofenac transdermal patch (DTP) versus diclofenac oral tablet (DOT) on the PEP level and OHRQOL in patients having symptomatic irreversible pulpitis with apical periodontitis and in mandibular molars following SVRCT. The null hypothesis is that there is no difference between DTP and DOT on the PEP level and OHRQOL.

Diclofenac sodium, chemical name is sodium 0-dichloroanilinophenylacetate, also known as diclofenac, and it is white crystalline powder, odorless, easily soluble in acetone, soluble in methanol and ethanol, slightly soluble in water, and it has hygroscopicity. Diclofenac sodium is the most important intermediate in diclofenac drugs. Because of its good anti-inflammatory and analgesic

effect and safety, it is widely used in the clinical treatment of various arthritis and other joint pain, neuralgia, whole body pain and all kinds of inflammation caused by the fever effect is good, so it is the common anti-inflammatory drug in the market

Chemical and physical properties

Its molecular formula is C14H10C12NNaO2, and it has the following structural formula



DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of Voltaren® (diclofenac sodium enteric-coated tablets) and other treatment options before deciding to use Voltaren. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals

After observing the response to initial therapy with Voltaren, the dose and frequency should be adjusted tosuit an individual patient's needs.

For the relief of osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses (50 mg b.i.d. or t.i.d.,or 75 mg b.i.d.).

For the relief of rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses (50 mg t.i.d. orq.i.d., or 75 mg b.i.d.).

For the relief of ankylosing spondylitis, the recommended dosage is 100-125 mg/day, administered as 25 mg q.i.d., with an extra 25-mg dose at bedtime if necessary.

Different formulations of diclofenac [Voltaren® (diclofenac sodium enteric-coated tablets); Voltaren®-XR (diclofenac sodium extended-release tablets); Cataflam® (diclofenac potassium immediate-release tablets)] are notnecessarily bioequivalent even if the milligram strength is the same.

indications pain and inflammation in theumatic dis- ease (including juvenile idiopathic arthritis) and other musculoskeletal disorders, acute gout, postoperative pain

Voltaren is indicated:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis

- For acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis

CONTRAINDICATIONS

Voltaren (diclofenac sodium enteric-coated tablets) is contraindicated in patients with known hypersensitivity todiclofenac.

Voltaren should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions, and PRECAUTIONS, PreexistingAsthma).

Voltaren is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypassgraft (CABG) surgery (see WARNINGS).

Pharmacokinetics

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available (see Table 1). Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of <20%.

Table 1. Pharmacokinetic Parameters for Diclofenac

PK Parameter	Normal Healthy Adults (20-48 yrs.)	
	Mean	Coefficient of Mean Variation (%)
Absolute Bioavailability (%) [N = 7]	55	40
T_{max} (hr) [N = 56]	2.3	69
Oral Clearance (CL/F; mL/min) [N = 56]	582	23
Renal Clearance (% unchanged drug in urine) [N = 7]	<1	—
Apparent Volume of Distribution (V/F; L/kg) [N = 56]	1.4	58
Terminal Half-life (hr) [N = 56]	2.3	48

Distribution

The apparent volume of distribution (V/F) of diclofenacsodium is 1.4 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 μg/mL)achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5- hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'• hydroxy-4'- methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However,

diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion.

One diclofenac metabolite 4'-hydroxy- diclofenac has very weak pharmacologic activity.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged

Side effects

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease orrisk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.
Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV eventsand the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase therisk of serious GI events.Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days

following CABG surgery found an increased incidence of myocardial infarction and stroke.

Hypertension

NSAIDs, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Voltaren® (diclofenac sodium enteric-coated tablets), should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema Renal Effects

Fluid retention and edema have been observed in some patients taking NSAIDs. Voltaren should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects:

Risk of GI Ulceration, Bleeding, and Perforation NSAIDs, including Voltaren, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be

fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% ofpatients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status.

Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective doseshould be used for the shortest possible duration.

Patients and physicians should remain alert for signs andsymptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Caution should be used when initiating treatment withVoltaren in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity hasalso been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose- dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate

overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of Voltaren in patients with advanced renal disease. Therefore, treatment with Voltaren is not recommended in these patients with advanced renal disease. If Voltaren therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with Voltaren. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [ULN = the upper limit of the normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in allstudies) occurred in about 2% of approximately patients at some time during diclofenac treatment. 5,700

In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In post marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and

in some cases, the first 2 months of therapy, but can occurat any time during treatment with diclofenac.

Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalitiesor liver transplantation.

Physicians should measure transaminases periodically in patients receiving long- term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminasemeasurements are not known.

Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac.

However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), Voltaren should be discontinued immediately.

To minimize the possibility that hepatic injury will becomesevere between transaminase measurements, physicians

should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Voltaren.

Voltaren should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin orother NSAIDs.

Skin Reactions

NSAIDs, including Voltaren, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, Voltaren should be avoided because it may cause premature closure of the ductus arteriosus

Drug Interactions

Aspirin: When Voltaren is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs,concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbitkidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: Voltaren, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Voltaren may increase cyclosporine's nephrotoxicity. Caution should be used when Voltaren is administered concomitantly with cyclosporine.

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide: Clinical studies, as well as postmarketing observations, have shown that Voltaren can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS, Renal Effects), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugstogether have a risk of serious GI bleeding higher thanusers of either drug along

Pharmaceutical form

Diclofenac sodium can be administered orally as a tabletor suspension, intramuscular in solution, intravenous in solution, transdermal in gel, or rectal routes

Dental uses

.Diclofenac is used to relieve mild to moderate pain and swelling (inflammation) from various conditions such as headache, dental pain and menstrual cramps.Some brands of this medication may also reduce pain, swelling, and joint stiffness from arthritis

Postendodontic pain was substantially reduced by preoperative administration of single oral dose of diclofenac sodium. It is thus possible to conclude that these favorable results might help to prevent postendodontic pain, especially in patients with a low pain threshold

Is diclofenac good for tooth extraction?

Conclusion: It can be concluded that diclofenac 50mg + paracetamol 500 mg and paracetamol 500 mg alone are found to be effective in the management of dental pain following tooth extraction with need of rescue medication

Dentists should consider nonsteroidal anti- inflammatory analgesics as the first-line therapy for acute pain management. Dentists should recognize multimodal pain strategies for management for acute postoperative pain as a means for sparing the need for opioid analgesics

Can diclofenac sodium be used for tooth pain?

Depending on why you're taking diclofenac, you may only need to take it for a short time. For example, if you have a sore back or toothache, you may only need to take diclofenac for 1 or 2 days. You may need to take it for longer if you have a long-term condition, such as rheumatoid arthritis Risk

Cardiovascular Risk

NSAIDs may cause an increased risk of serious •
cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or

risk factors for cardiovascular disease may be at greaterrisk.

- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms.
Elderly patients are at greater risk for serious gastrointestinal events.

Management :

Descriptions. Diclofenac is a nonsteroidal anti- inflammatory drug (NSAID) used to treat mild-to- moderate pain, and helps to relieve symptoms of arthritis (eg, osteoarthritis or rheumatoid arthritis), such as inflammation, swelling, stiffness, and joint pain

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should alsobe encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Voltaren, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprisedof the importance of this follow-up

2. Voltaren, like other NSAIDs, can cause GI discomfort and, rarely, more serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis.

Patients should be apprised of the importance of this follow-up, Gastrointestinal Effects: Risk ofUlceration, Bleeding, and Perforation).

.3 Voltaren, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, whichmay result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

.4 Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

.5 Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant
tenderness, and “flu-like” symptoms). If these occur,
patients should be instructed to stop therapy and seek immediate medical therapy

Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling

of the face or throat). If these occur, patients should be instructed to seek immediate emergency help

In late pregnancy, as with other NSAIDs, Voltaren .7
should be avoided because it will cause premature closure of the ductus arteriosus.

Pregnancy

Teratogenic Effects: Pregnancy

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are

not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should beavoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survivaloccurred. The effects of Voltaren on labor and delivery inpregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Voltaren, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have notbeen established.

Geriatric Use

As with any NSAIDs, caution should be exercised intreating the elderly (65 years and older).

ADVERSE REACTIONS

In patients taking Voltaren® (diclofenac sodium enteric- coated tablets), or other NSAIDs, the most frequently reported adverse experiences occurring in approximately1%-10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionallyinclude:

Body as a Whole: fever, infection, sepsis

Cardiovascular System: congestive heart failure,hypertension, tachycardia, syncope

Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis,thrombocytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities,

drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo Respiratory System: asthma, dyspnea

Skin and Appendages: alopecia, photosensitivity, sweatingincreased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes,
death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, eructation, liver failure,pancreatitis

Hemic and Lymphatic System: agranulocytosis, hemolytic anemia, aplastic anemia,

lymphadenopathy, pancytopenia Metabolic and

Nutritional: hyperglycemia

Nervous System: convulsions, coma, hallucinations,meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment

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