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Pharmaceuticals and Toxicology of Local Anaesthetics

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ABSTRACT:

The greatest significant achievement in dentistry science during the past 100 years may have been the creation of safe and efficient local anaesthetic drugs. The modern dental agents are quite safe and meet the majority of the criteria for an excellent local anaesthetic. These local anaesthetic substances can be used with little risk of causing tissue irritation or adverse responses. There are numerous substances that offer quick onset and sufficient duration of surgical anaesthetic. The drugs offer totally reversible anaesthesia, and systemic toxicity is infrequently recorded. There is currently no perfect local anaesthetic drug that can selectively inhibit pain pathways to cause localised analgesia without affecting the transmission of other sensory modalities.

This issue of Dental Clinics of North America gives a summary of recent developments in local anaesthetic therapies that are now employed in dentistry and sheds light on a variety of issues regarding the substances used for local anaesthesia. In this introduction, the clinical pharmacology of the current local anaesthetic drugs and formulations used in dentistry is briefly updated. This update is followed by a discussion of the dosing methods required to avoid local anaesthetic toxicity reactions.

Keywords*:* Pharmaceuticals, Toxicology, Anaesthetics

INTRODUCTION:

A majority of amides have been employed as local anaesthetic agents in dentistry for the past 20 years. Two of the most widely used amide local anaesthetics in dentistry, lidocaine and mepivacaine, have a 50-year track record of efficiency and safety in administering regional anaesthesia for dental therapy. The reason why doctors prefer amide local anaesthetics over ester anaesthetics (such as procaine and propoxycaine) is because amides deliver profound surgical anaesthesia more quickly and reliably while causing fewer sensitising reactions. The development of many of the complex surgical outpatient treatments that are now available in dentistry has been made possible by the availability of different dental formulations of amide agents that give anaesthesia of varying duration. [1]

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Different chemical properties of their molecular structures can be used to explain variations in the clinical characteristics of local anaesthetic drugs. The pH at which a drug's ionised (charged) and nonionized (uncharged) forms are present in equal amounts is determined by its dissociation constant (pKa). This value is crucial for efficient anaesthesia because local anaesthetic molecules must be in their uncharged form in order to diffuse across lipid nerve sheaths and cell membranes. In contrast, only the charged form may diffuse through internal cytoplasm and extracellular fluid, as well as dissolve in water. In order to determine an agent's diffusion qualities and, thus, the pace of onset, its pKa is crucial.

At a typical tissue pH of 7.4, procaine, which has a pKa of 8.9, is 98% ionised. Most of the molecules remain in their charged condition at normal pH after procaine injection, making them incapable of crossing cell membranes. Procaine and other ester local anaesthetics therefore have an unacceptable delay in the onset of anaesthesia. Amide anaesthetics with pKa values between 7.6 and 8.0 have a lower concentration of the drug in an ionised form, diffuse through tissue more easily, and have tolerably quick onset times. [2–4]

The features of a local anesthetic's lipid solubility that best predict its effectiveness. While bupivacaine is extremely lipid soluble and most potent, procaine is one of the least lipid-soluble and least potent local anaesthetics. The length of anaesthesia is primarily determined by the protein binding properties. It is less likely for substances to diffuse from the site of action and reach the systemic circulation when they bind to protein elements of neuronal membranes. The substantial differences in their capacities to bind proteins account in part for the short duration of lidocaine's activity and the prolonged duration of bupivacaine's action. [2,5]

It is apparent that the clinical qualities of local anaesthetics are influenced by lipid solubility, ionisation, and protein binding capabilities. However, additional parameters that affect the clinical performance of a local anaesthetic include the injection site, drug and vasoconstrictor concentration, injection volume, and the anesthetic's natural vasodilating qualities.

Local Anesthetics: Current Practice

Dental anaesthetic formulations including ester agents are no longer sold because they are less effective at inducing anaesthesia than amides and because they are more likely to produce allergic responses. In the US, lidocaine is still the most widely used local anaesthetic. Articaine formulations have eclipsed lidocaine in popularity in Canada, making them the most often used dental anaesthetic. Bupivacaine, a long-acting local anaesthetic, is frequently used to treat postoperative pain, according to a US oral surgeon survey on preferred local anaesthetic medications. Mepivacaine with 1:20,000 levonordefrin (Neo-Cobefrin), lidocaine with 1:50,000 epinephrine, 3% mepivacaine plain, and 4% prilocaine plain were among the formulations utilised by less than 2% of the oral surgeons surveyed. [6]

Procaine and propoxycaine, two ester anaesthetics, were combined and sold as dental cartridges up until 1989. This mixture contained 0.4% propoxycaine (Ravocaine), 2%

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procaine (Novocain), and a vasoconstrictor at a ratio of 1:20,000. Because they have weak diffusion qualities, ester anaesthetics are typically less efficacious than amides. Because it is a strong vasodilator, procaine is ineffective when administered alone. The hydrolysis of esters by plasma and tissue esterases results in the production of para-aminobenzoic acid (PABA) and diethylamino alcohol. The allergen that appears to be connected to procaine's considerable allergenicity is PABA. In a companion piece published elsewhere in this issue, Speca and colleagues address the issue of patients reporting allergies to local anaesthetics.

Lidocaine hydrochloride

Since its introduction into clinical use in the 1950s, lidocaine has established itself as the standard dental local anaesthetic in North America due to its exceptional efficacy and safety. In addition to having great anaesthetic efficacy, lidocaine has a low allergenic potential; in the past 50 years, there have been less than 20 confirmed cases of serious allergic anaphylactic reactions (also known as anaphylactoid). The infrequent occurrence of severe, life-threatening hypersensitivity responses linked to lidocaine is a crucial clinical advantage given the widespread use of local anaesthetic in dentistry (500,000–1,000,000 injections each day across the United States and Canada).

In cartridges, lidocaine comes in three different formulations: 2% lidocaine plain, 2% lidocaine with 1:50,000 epinephrine, and 2% lidocaine with 1:100,000. The combination of 2% lidocaine and 1:100,000 epinephrine is regarded as the benchmark when assessing the efficacy and security of more recent anaesthetics.

Mepivacaine hydrochloride

Mepivacaine plays a significant role in dental anaesthesia since it can induce substantial local anaesthetic without being compounded with a vasoconstrictor like epinephrine or levonordefrin and has minimally dilating characteristics. A significant tool for a dentist's toolbox is the availability of a 3% mepivacaine formulation without a vasoconstrictor. Dental cartridges containing 2% mepivacaine with 1:20,000 levonordefrin or 3% mepivacaine plain are available.

Mepivacaine plain may be helpful in paediatric dentistry since kids are known to chew their lips following dental treatments. It is frequently claimed that mepivacaine plain has a shorter duration of soft tissue anaesthetic. But according to one study, the duration of soft tissue anaesthetic for mepivacaine and lidocaine with epinephrine is about the same, despite the pulpal durations of mepivacaine plain being shorter than those of 2% lidocaine with epinephrine. [7] Alternately, utilising the a-adrenergic receptor antagonist phentolamine, it has been demonstrated that the time that soft tissue anaesthetic lasts following a dental surgery is reduced. In another paper in this issue, Hersh and Lindemyer discuss local anaesthesia reversal, a recent development in dental anaesthetic therapeutics.

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Prilocaine hydrochloride

Similar to mepivacaine, prilocaine is not a strong vasodilator and can be used with or without a vasoconstrictor to produce effective oral anaesthetic. It comes in 4% prilocaine plain and 4% prilocaine with 1:200,000 epinephrine formulations. The epinephrine-containing formulation resembles 2% lidocaine with 1:100,000 epinephrine in terms of its anaesthetic properties. The duration of surgical anaesthetic is marginally shortened with the 4% prilocaine simple formulation. The pH of the prilocaine simple solution found in dental cartridges is a little less acidic. Clinical research have not proved this, but there is some evidence that prilocaine causes less pain during injection. [8]

One of the metabolic byproducts of prilocaine has been linked to the emergence about methemoglobinemia. Benzocaine, a topical anaesthetic, overdoses have also been linked to methemoglobinemia. The importance of this negative outcome is addressed in a different essay in this issue by Trapp and Will.

Articaine hydrochloride

Articaine is categorised as an amide anaesthetic, like the majority of dental anaesthetics available to dental professionals. With a thiophene (sulfur-containing) ring and an ester side chain, articaine has a rather distinctive molecular structure. Articaine is quickly rendered inactive by hydrolysis of the ester side chain to articainic acid as it is absorbed from the injection site into the systemic circulation. As a result, among the anaesthetics used in dentistry, articaine has the lowest metabolic half-life (estimated to be between 27 and 42 minutes). [9,10] Dental cartridges are available with formulations comprising 4% articaine hydrochloride with 1:100,000 epinephrine and 4% articaine with 1:200,000 epinephrine. Studies comparing articaine to 2% lidocaine with 1:100,000 epinephrine have consistently concluded that articaine's onset time, duration, and anaesthetic profundity are comparable to those of mandibular block and maxillary infiltration anaesthesia. [11–16] In another paper in this issue, Paxton and Thome provide a thorough analysis of the relative efficacy of lidocaine and articaine formulations. Because the ester metabolite of articaine is not the allergen PABA, it does not appear to be more allergic than other amide anaesthetic agents already on the market.

There are very few reports of harmful effects following the use of articaine for dental anaesthetic. The apparent lack of overdose effects following its administration may be explained by the quick inactivation of articaine by plasma esterases. The inferior alveolar and lingual nerves have been linked to articaine and prilocaine paresthesias. Moore and Haas write about this contentious subject in another piece in this issue. The argument that articaine has superior diffusion capabilities and that anaesthesia can be induced following buccal infusion in the mandible is supported by a growing body of clinical research material. A critical evaluation of articaine's effectiveness to deliver mandibular pulpal anaesthetic following buccal infiltration may be found in another article by Meechan in this issue.

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Bupivacaine hydrochloride

The long-acting amide local anaesthetic bupivacaine has been a staple in dentists' toolkits over the past few decades. This long-acting medication is quite helpful in the overall control of the surgical postoperative pain related to dental care. 6 Bupivacaine (1-butyl-2',6'-pipecoloxylidide) shares the same molecular structure as mepivacaine, with the exception of a butyl (4 carbon) group replacing the methyl (1 carbon) group at the amino terminus of the molecule. Mepivacaine's molecular structure includes a butyl group, which improves its ability to bind to proteins and dissolve in lipids. [17,18] Bupivacaine may offer sufficient surgical anaesthetic, but its greatest utility is in the treatment of postoperative pain. [19,20] According to clinical studies, bupivacaine has a significantly slower onset time than traditional amide anaesthetics due to its elevated pKa of 8.1. When epinephrine is added to bupivacaine formulations, onset timings and profundity are improved. [5,21]

Using a nonsteroidal anti-inflammatory medicine before to surgery along with a long-acting anaesthetic may help maximise patient comfort when controlling postoperative pain. 22 Another review article in this issue by Gordon and Dionne focuses on the use of long-acting local anaesthetics to treat postoperative and ongoing pain.

TOXICITY REACTIONS ASSOCIATED WITH LOCAL ANESTHESIA:

For dental practise, a dentist must be able to safely provide local anaesthetic. The formulation of local anaesthetic solutions used in North America for dental anaesthesia includes an amide local anaesthetic, an adrenergic vasoconstrictor, and a sulfite antioxidant (ester local anaesthetic medicines are no longer accessible in dental cartridges). Any of these ingredients may cause systemic, dose-dependent adverse effects in vulnerable persons. Although exceedingly unusual, allergic and hypersensitive reactions to local anaesthetics and sulfites can occasionally happen (for more information on this subject, see the article by Speca and colleagues elsewhere in this issue). The specific signs and symptoms of methemoglobinemia, among other adverse reactions to local anaesthetics, allow for quick identification and treatment. An essay by Trapp and Will elsewhere in this issue offers a critical evaluation of acquired methemoglobinemia. Rapid injection of substances that contain an adrenergic vasoconstrictor can result in significant cardiovascular stimulation.

When correctly managed, serious responses are relatively uncommon and unlikely to cause severe morbidity or fatality. Toxicities brought on by relatively high local anaesthetic or vasoconstrictor dosage are the most severe and lethal of adverse responses. With adequate patient assessment and dosage estimates, these responses can be avoided. The anaesthetic drug in a dental cartridge is absorbed into the systemic circulation after diffusing away from the injection site, where it is digested and removed. Dental local anaesthetic often only requires small doses, and it is relatively rare for the medicine to have systemic effects after being ingested. However, blood levels of a local anaesthetic may become dramatically raised if an accidental vascular injection occurs, if repeated injections are given, or if relatively high

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amounts are utilised in paediatric dentistry. Epinephrine can greatly lessen the absorption of local anaesthetics when added to formulations.

Toxicity Reactions to Excessive Local Anesthetic Dose

Initial signs of local anaesthetic overdose include excitatory symptoms such tremors, muscle twitches, shivering, and clonic-tonic convulsions. [23–25] The central nervous system's limbic system's early excitatory responses are assumed to be disinhibition phenomena brought on by the selective blockage of tiny inhibitory neurons (CNS). 2 If blood concentrations of the local anaesthetic drug keep rising, whether this initial excitatory reaction is visible or not, a broad CNS depression with signs of sedation, drowsiness, lethargy, and life-threatening respiratory depression follows. Myocardial excitability and conductivity may also be reduced at extremely high lethal dosages, particularly when the highly lipid-soluble long-acting local anaesthetic bupivacaine is used. 26 Ectopic cardiac rhythms and bradycardia are the most frequent symptoms of cardiac toxicity after local anaesthetic overdose. Extreme local anaesthetic overdoses result in peripheral vasodilation and decreased cardiac contractility, which significantly lower blood pressure.

The first and most crucial step in preventing this adverse event is to follow the instructions for administering local anaesthetic dosage. Calculations for dosage are based on the supplied substance and the patient's body weight in order to prevent systemic reactions to local anaesthetics. Pediatric patients are the ones that experience true dose-dependent adverse reactions to local anaesthetics the most commonly. [23–25]

Following is an example of a case report of a local anaesthetic toxicity reaction in paediatric dentistry:

“A series of extractions were planned for a healthy five-year-old girl patient who weighed 36 lbs. A nasal mask was used to administer N2O/O2 sedation to the youngster. Five cartridges of 3% mepivacaine were then injected into the infant's maxilla and mandible (270 mg). The child suffered "stiffening and shaking" of all of their extremities for ten seconds ten minutes later. Following another two convulsive episodes, there was a cardiopulmonary arrest. Resuscitation attempts and transportation to a nearby hospital were unsuccessful. Four days later, there was a death. [27]”

Due to the child's reduced stature, the amount of local anaesthetics must be decreased while giving them. According to Clark's rule, the dosage adjustment for children should be computed as a percentage of the child's body weight, as in the following formula: child's dose = 5 [child's weight/adult weight] [adult dose]. The dose for the youngster in the case study that was previously presented should have been reduced by 24 percent, or 36 pounds per 150 pounds. Due to the fact that a child's smaller body weight does not correspond to a commensurate drop in orofacial morphology, toxicity reactions in children may happen more frequently. There is an apparent requirement to utilise significantly higher amounts while inducing local anaesthetic in juvenile dental patients since the mandible and maxilla of a

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child weighing 36 lb are only 50% to 60% the size of an adult (weighing 150 lb). As a result of this discrepancy, children are more likely to experience local anaesthetic toxicity reactions. Children also have a higher risk of developing systemic medication interactions with the local anaesthetics and other CNS-depressants used for paediatric sedation. [23,24]

There are an unusually high number of cases of local anaesthetic toxicity that appear to be related to the local anaesthetic formulation of 3% mepivacaine plain. [23–25,27–29] This toxicity might result from the absence of a vasoconstrictor, which would have sped up the anesthetic's absorption into the body. Additionally, the administration of larger relative dosages might be necessary due to the drug's increased concentration (3%) in its anaesthetic formulation. After maxillary infiltration injections, Goebel and colleagues' pharmacokinetic studies30,31 showed that peak anaesthetic blood levels of 3% mepivacaine occur more quickly and are higher by about three times than those of a similar volume of 2% lidocaine with 1:100,000 epinephrine. [30,31]

Vasoconstrictors can control both the initial rise in local anaesthetic medication levels and their ultimate peak. Following the administration of lidocaine alone as opposed to lidocaine combined with epinephrine, a greater peak serum concentration can be observed. Since lidocaine with epinephrine has a higher maximum recommended dosage (MRD), the maximum recommended dose (MRD) for lidocaine alone is lower (300 mg for an adult) (500 mg for an adult). Local anaesthetic mepivacaine has less vasodilating effects than lidocaine.

As a result, there are fewer noticeable changes in serum levels between mepivacaine formulations that contain and do not contain a vasoconstrictor. Youngsters frequently receive dental local anaesthetic with the 3% mepivacaine formulation because it is thought to have a shorter duration of soft tissue anaesthesia, which limits severe lip-biting and mouth injuries in children. However, a double-blind randomised trial's findings revealed that soft tissue anesthesia's onset time, peak effects, and duration were quite comparable following injections of 2% lidocaine with 1:100,000 epinephrine, 3% mepivacaine plain, or 4% prilocaine plain into the mandibular block. 7 For kids, using anaesthetic formulations without a vasoconstrictor—like 3% mepivacaine—might not offer a meaningful therapeutic benefit.

Conflicting published dosage recommendations available in the literature and the multiple units used in the computation make determining MRDs for kids receiving local anaesthetics difficult (milligram, percentage, cubic centimeter, milliliter, kilogram, pound, cartridges). The most recent reliable sources are probably the MRDs for dental local anaesthetics taken from manufacturers' package inserts and published in the American Dental Association's reference to dental therapeutics. For lidocaine and epinephrine, these recommendations allow the use of the maximum amount, while for mepivacaine and articaine, the smallest volume. Additionally, the long-acting local anaesthetic bupivacaine is typically not recommended for young children in order to prevent oral damage following dental anaesthetic. [32]

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The most limiting local anaesthetics used in dentistry have maximum volumes of 3% mepivacaine plain for an anaesthetic injection (7.4 cartridges for a 150 lb adult) and 4% articaine with epinephrine (6.9 cartridges for a 150 lb adult). 2% lidocaine with epinephrine has a maximum capacity that allows the most amount to be administered safely (14 cartridges for a 150 lb adult). If numerous injections are necessary, the formulation of 2% lidocaine and 1:100,000 epinephrine is the least likely to result in hazardous reactions in children.

The most conservative rules that can be applied to all anaesthetic formulations used in dentistry have been developed as a result of the establishment of a simplified alternative for determining the maximum acceptable doses of local anaesthesia (Table 4). According to these recommendations, known as "the Rule of 25," a dentist may use one cartridge of any commercially available local anaesthetic for every 25 pounds of a patient's weight, which translates to one cartridge for a patient weighing 25 pounds, three cartridges for a patient weighing 75 pounds, and six cartridges for a patient weighing 150 pounds or more.

Management of Local Anesthetic Overdose

The most typical sign of a genuine overdose situation is tonic-clonic convulsions. Convulsions brought on by a local anaesthetic are often brief. Loss of consciousness and severe, protracted respiratory depression are likely to follow a convulsive episode.

Convulsions and a possible respiratory depression should both be treated as emergencies right away. The patient must be safeguarded from harm, placed in the supine position, have the airway maintained, and have their vital signs monitored, particularly their respiratory adequacy. Positive pressure oxygen breathing is crucial if the patient is unresponsive and experiencing respiratory arrest. Convulsions brought on by local anaesthetic are often brief, therefore administering an anticonvulsant like intravenous diazepam in doses of 5 to 10 mg is rarely necessary.

Toxicity Reactions to Excessive Vasoconstrictors Dose

The two catecholamine vasoconstrictors that are used with local anaesthetics in dental cartridges are epinephrine and levonordefrin. The addition of a vasoconstrictor can increase the formulation's safety by reducing the local anesthetic's systemic absorption and lowering its peak blood levels.

After submucosal injection of one or two anaesthetic cartridges containing epinephrine or levonordefrin, the circulatory system is only mildly stimulated. However, high dosages of these adrenergic vasoconstrictors or accidental intravascular administration of the drugs can stimulate the cardiovascular system, leading to clinically substantial elevations in blood pressure and heart rate. For instance, it was discovered that administering 7 cartridges of 4% articaine with 1:100,000 epinephrine increased systolic blood pressure by 6 mm Hg and the average heart rate by 9 beats per minute (bpm), from 69 to 78 bpm (from 125 to 131 mm Hg). [10] It was once believed that the modest amount of epinephrine in a dental cartridge couldn't

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considerably raise epinephrine blood levels following local anaesthetic delivery. After the delivery of local anaesthesia, the majority of the reported cardiovascular stimulation was considered to be caused by the patient's worry and anxiety or the pain of the injection. The epinephrine in just 2 cartridges of 1:100,000 formulations, according to research, can considerably raise circulating epinephrine levels. To ascertain the degree to which the increase in total epinephrine plasma levels was caused by the supplied tritium-labeled epinephrine, Lipp and colleagues [33 injected 2 mL of 4% articaine containing tritium-labeled epinephrine (1:100,000). The total epinephrine levels increased with submucosal injections (16 individuals), rising from a baseline level of 200 pg/mL to a peak level of 631 pg/mL at 7 minutes. The tritium-labeled epinephrine that was administered was primarily responsible for the rise in total epinephrine levels. Four participants had apparently accidental intravascular local anaesthetic injections, which resulted in a minute-long increase in epinephrine levels to a mean peak level of 2645 pg/mL. Some of these patients were found to have significant cardiovascular stimulation, as evidenced by tachycardia and extrasystoles, even if this rise was only temporary. It is obvious that extremely high doses or unintentional intravascular injections might cause clinically severe cardiovascular reactions. Common recommendations to avoid rapid systemic absorption of epinephrine and levonordefrin include utilising anaesthetic formulations with no or low doses of vasoconstrictors, slow injection techniques, and careful, repeated aspiration.

If a patient's medical history shows considerable cardiovascular impairment, the use of vasoconstrictors may need to be restricted. Although vasoconstrictors are rarely contraindicated, dental professionals should try to steer clear of formulations that contain them if at all possible due to the potential activation of the circulatory system after intravascular injections. When a vasoconstrictor is necessary for dental treatment and there is a medical history that suggests a need for prudence, it is frequently advised to keep the epinephrine dose to 0.04 mg. 34 One of the following complete anaesthetics can be used to achieve this dose reduction:

- One anaesthetic cartridge with a 1:50,000 epinephrine dosage
- Two anaesthetic cartridges with a 1:100,000 epinephrine content
- Four anaesthetic cartridges with an epinephrine concentration of 1:200,000.

Additionally, when utilising local anaesthetics that contain the vasoconstrictors levonordefrin and epinephrine, practitioners need to be aware of medication interactions. According to earlier studies, patients taking nonselective b-adrenoreceptor blockers, tricyclic antidepressants, cocaine, and a-adrenergic blockers should take vasoconstrictors with caution. [35] Exaggerated systemic vasoconstrictive reactions to epinephrine or levonordefrin may occur in patients using nonselective b-adrenergic antagonists like propranolol. [17] In another paper in this issue, Hersh and Giannakopoulos provide a critical analysis of this medication interaction.

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In patients who are pregnant, using local anaesthetics with vasoconstriction-containing drugs may raise additional safety concerns. Another article by Fayans and colleagues in this issue reviews this potential risk and offers therapeutic suggestions for this unique demographic.

CONCLUSION:

The amide local anaesthetics used in dentistry nowadays are very secure and efficient. Lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine are all available in a variety of formulations, allowing a practitioner to choose the ones that best suit their patient's needs. The treatments and arsenal of local anaesthetic have made significant strides in recent years, making them available to dental professionals. Most severe adverse reactions to dental local anaesthetic agents can be avoided through careful agent selection and dosage adjustment.

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