NON-STEROIDAL ANTI-INFLAMMATORY DRUGS:

PHENYLBUTAZONE AND OTHERS

by

Thomas Tobin, MRCVS, PhD

Author's Address: Department of Veterinary Science, Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, KY 40546-0099

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SUMMARY

Phenylbutazone is the principal member of the non-steroidal anti-inflammatory (NSAID) group of drugs used in equine therapeutics. These drugs are all acidic in nature, require administration in relatively high doses, and act by inhibiting prostaglandin formation. They generally attain peak activity within two to four hours of intravenous administration or later after oral administration. Their actions are largely terminated by metabolism, and they are found in blood or urine as parent drug, or as metabolites, for several days after drug administration.

The absorbtion, disposition, and elimination kinetics of phenylbutazone have been studied in some detail. Absorbtion of phenylbutazone from the intestinal tract is slow and is affected by both the dosage form and the presence or absence of feed in the horse's intestinal tract. Once absorbed the plasma half-life of phenylbutazone is affected by the plasma level of the drug in a manner described as dose-dependent kinetics. This means that the higher the plasma level of the drug the slower its elimination. This leads to circumstances in which the concentrations of drug in the blood can rise relatively rapidly and give rise to toxicity.

Toxicity due to phenylbutazone can occur within days. Signs of toxicity include anorexia, depression, oral and gastro-intestinal ulcers, plasma protein losing enteropathy, and death from shock. Other side effects include toxic neutropenia, hepatotoxicity, and renal papillary necrosis. If phenylbutazone is withdrawn in the early stages of toxicity the prognosis is good.

The therapeutic effects of phenylbutazone are best described by the phrase "reduction of soft tissue inflammation." Phenylbutazone can be administered to animals before surgery, to animals with tissue tears and lacerations, or to animals with soft tissue injury. While in these cases

the inflammatory response is non-infective, the drug may as an adjunct to antibiotic therapy be used in association with infective inflammation.

Phenylbutazone and the other NSAID drugs have no direct effect on pain perception but rather act to reduce the hypersensitivity to pain caused by the inflammatory response. It is this reduction of the inflammatory component of pain and their ability to reduce soft tissue inflammation that makes phenylbutazone and its congeners so useful in performance horses.

INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAID) all share a number of properties which seem to be required for their anti-inflammatory action (Figure 1). All are acidic drugs, with a pKa of 4.5 or less. The acidic nature of these drugs means that they are all between 95% and 99% bound to plasma proteins. Because of this, drugs of this group do not pass into saliva, and saliva testing is essentially useless for detection of this important group of drugs. Their acidic nature also seems to be important for their action and has led to suggestions that their acidity enables them to accumulate in inflamed tissues, which also tend to be acidic. This accumulation would then allow them to have more effect in inflamed areas than in normal tissue. However, these agents also tend to accumulate in the stomach, small intestine and kidney, and we will see later that the toxicities produced by these agents are usually associated with these tissues. Also, because prostaglandins are involved in the generation of fever, all these drugs are antifever and antipyretic agents (Figure 2) (Tobin et al., 1986).

Phenylbutazone and the other nonsteroidal antiflammatory drugs produce their anti-inflammatory effects by inhibiting the production of chemicals called "prostaglandins." Prostaglandins are produced in larger amounts in inflamed tissues and are involved in the blood vessel changes which cause

the reddening, heat, swelling, pain and loss of function that we associate with inflammation. They also have another peculiar action, in that they act to sensitize pain receptors in the inflamed area to agents which cause pain. Anybody who has had anything as simple as a good sunburn is familiar with the great increase of sensitivity to even the lightest touch which occurs in sunburned tissue. This hypersensitivity is a typical effect of certain prostaglandins. In fact, if minute amounts of prostaglandins are injected into a normal joint, that joint soon becomes excruciatingly painful to move. It is clear from this mechanism of action that if the concentration of prostaglandins in inflamed tissues can be reduced, the signs of inflammation, swelling, and particularly the perception of pain in that area will also be reduced. This ability of the phenylbutazone-like drugs to reduce the cardinal signs of inflammation leads directly to the clinical uses of phenylbutazone and its congeners.

CLINICAL USES

The several clinical uses of phenylbutazone in veterinary medicine are encompassed by the phrase 'reduction of soft tissue inflammation'. Phenylbutazone can be administered to animals before surgery, to animals with tissue tears or lacerations, or other tissue trauma (Oehme, 1962), or to animals with soft tissue injuries associated with racing or other performance events. In all these instances, the inflammatory response is non-infective, so that phenylbutazone alone is effective. The drug may be useful in septic soft tissue inflammation as well, although it should be used in association with anti-infective (antibiotic) medication. Much of the early work with phenylbutazone demonstrates this suppression of soft tissue inflammatory responses (Tobin, 1981).

It is important to keep in mind that phenylbutazone and other NSAIDs have no direct effect on pain perception, but act to reduce hypersensitivity

to pain by reducing the inflammatory response. They therefore have no effect on pain perception in non-inflamed tissues. NSAIDs such as phenylbutazone are therefore effective against the dull throbbing pain of inflammation, but not against sharp stabbing pains, which are produced by the direct stimulation of sensory nerves. This characteristic of the action of phenylbutazone is often misunderstood by laymen, who assume that phenylbutazone supresses the baseline perception of pain in much the same way as the narcotic analgesics and local anesthetics supress pain perception. This is clearly not the case, and it is important to distinguish clearly between the actions of NSAIDs on pain and those of other medications used to control pain.

In a series of experiments in my laboratory we clearly distinguished between the actions of the local anesthetics and phenylbutazone on pain perception in normal tissues. As shown in Figure 3, phenylbutazone had no effect whatsoever on pain perception for 24 hours after a 7.3 mg/kg IV dose, while a nerve block induced by mepivacaine (Figure 4) had a dramatic effect on pain perception, blocking it essentially completely for up to three hours. Phenylbutazone thus had no effect on pain perception in normal cutaneous tissue, a finding that is consistent with the concept that it acts to reduce the formation of prostaglandins only in inflamed tissue (Kamerling et al., 1985).

The actions of phenylbutazone on soft tissue inflammation are of particular value in the performance horses. In inflamed joints, more than 99% of the resistance to movement is due to soft tissue inflammation. Reduction of soft tissue inflammation largely eliminates this resistance, and thus largely restores normal joint function.

The basis for the action of phenylbutazone on degenerative joint disease and osteoarthritic joint disease is less clear. Phenylbutazone is unlikely

to affect long-standing degenerative articular or bony change in or around joints that reportedly characterize most cases of 'racetrack' lameness. Further, there are no pain receptors in articular cartilage. Nevertheless, phenylbutazone is apparently useful in both osteoarthritic joints and degenerative joint disease. While these effects may be due to actions of phenylbutazone on the relatively permanent structural changes seen in these conditions, it seems much more likely that the therapeutic responses are attributable to effects of phenylbutazone on soft tissue changes associated with these conditions.

In man, phenylbutazone is particularly effective in the enthesopathies, in which tendon insertions become swollen and inflamed. Ankylosing spondylitis is the best known of these conditions. To our knowledge, enthesopathies are not recognized as a clinical entity in the horse.

In racetrack practice in the USA, the principal use of phenylbutazone is as an adjunct in the training of 'sore' horses. Horses with chronic arthritic and ligamentous problems also derive benefit. In some countries, the use of phenylbutazone to keep a horse in training and to enable it to race longer than in the absence of the drug is regarded as permissible, but others contend that it can never be acceptable to use phenylbutazone to allow an unsound horse to run. Some equine practitioners believe that horses race consistently on phenylbutazone, and that they race for longer. However, these views are controversial, and there is concern over possible hazards to the horse arising from this kind of prophylactic use..

Clinical conditions responding to phenylbutazone therapy include sore feet (pedal osteitis), cunean tendon bursitis (jacks), spavins, minor sprains and muscle soreness, splints, navicular disease, osselets and ringbones. Further, it is common practice for many horsemen to administer phenylbutazone after a race, as this is said to prevent the animals from

'cooling out sore'. Under these circumstances, when used with great care, phenylbutazone seems to be beneficial, and it may allow a horse to run up to his best form (Tobin, 1981).

Hamm (1978) administered the NSAID naproxen to about 50 quarterhorse yearling colts during their training and racing careers. Treated horses lost only 3% of their training time, compared with a 13% loss for non-treated animals. Similarly, when the treated groups reached the racetrack, they raced more often than the control group, and their injuries were reduced dramatically, by four-fold during training and by 30-fold during racing. These results suggest that there may be a case for using anti-inflammatory medication in training and racing horses, but others consider the conclusion controversial.

Although limited, the available experimental evidence may also support the horseman's contention that phenylbutazone allows a horse to 'run up to its potential'. Studying the action of drugs on performance, Sanford administered phenylbutazone to four horses and tested them 24 h later (Tobin, 1981). Sanford was surprised to find that performance was improved, and he could explain the improvement only by assuming that the horses, which he had considered sound, were actually subclinically lame. Similarly, J.-M. Jouany in France has proposed that small doses of the phenylbutazone improve the performance of horses, supporting the data of Sanford. One possible interpretation of these findings is that there is no such thing as a completely 'sound' horse, and that the closest approximation to this ideal is a 'clinically sound' horse treated with phenylbutazone.

Phenylbutazone has been given to breeding mares for long periods with little apparent effect on their ability to conceive or to carry foals to term. It has also been used at high dose rates in the treatment of endotoxin shock, when it relieves the acute symptoms of the condition, but has little effect on the final mortality associated with this syndrome.

Because of the widespread use of phenylbutazone in performance horses, its ability to influence performance, and the uncertainties surrounding the risks and benefits for the horse, the use of phenylbutazone in performance horses is a vigorously debated area. In general, the use of phenylbutazone in performance horses is a matter for the regulators of individual sports, rather than a question in clinical medicine, although the possible long-term effects on the well-being of the horse is the concern of clinical veterinarians.

DISPOSITION OF PHENYLBUTAZONE

Phenylbutazone, in addition to being well studied, has some of the most complicated pharmacokinetics of any drug commonly used in racing horses. To summarize these effects, its absorbtion from the gastrointestinal tract is variable, its plasma half-life is highly dose dependent and its concentrations in urine are highly pH dependent (Smith, et al., 1987).

Studying the factors affecting the absorbtion of phenylbutazone from the gastrointestinal tract, it appears that the bioavailability of the dosage form of the drug is of importance. Additionally, the presence or absence of feed in the gastrointestinal tract has a very important effect, with the presence of feed in the gastrointestinal tract delaying the time to peak drug concentration and reducing the area under the curve. In particular, ponies with free access to hay showed greatly delayed and reduced absorbtion of phenylbutazone. On the other hand, paste preparations have unusually high bioavailability, and individual horses have been shown to poorly absorb this drug, for reasons which are unclear.

Once phenylbutazone is absorbed into the blood stream of the horse its rate of excretion depends on plamsa levels of the drug. Thus the higher the blood levels of the drug, the longer the drug persists in the body and the

more likely the next dose of drug is to accumulate in the body. This phenomenon is called dose dependent kinetics, and it means that if the horse cannot readily excrete a dose of phenylbutazone that the next dose will "add" on top of the previous dose and the blood levels of phenylbutazone will rise. Based on these findings the optimal dose of phenylbutazone for a horse should not be in excess of two g/horse IV, and somewhat more orally, dependent on the bioavailability of the dosage form.

The urinary concentrations of phenylbutazone and its metabolites in the horse are determined largely by urinary pH. As an acidic drug phenylbutazone and its metabolites tend to trap in basic urine and the concentrations of phenylbutazone, oxyphenbutazone, and gamma-hydroxyphenylbutazone are greatly increased in basic urine. As shown previously the concentrations of these metabolites in basic urines can be up to 200 times the concentrations of acidic urines. The upshot of these circumstances is that it is very difficult to determine the times of administration of a drug simply by examination of a urine sample, since urinary pH appears to be the dominant factor in determining the urinary concentrations of phenylbutazone and its metabolites.

Because of the forensic need to quantitate phenylbutazone and its metabolites and the unsatisfactory nature of urinary quantitations, most US jurisdictions now quantitate blood levels of this drug, and 5 µg/ml is the most commonly recommended regulatory blood level of this drug. Unfortunately, however, no studies have been carried out to determine withdrawal times for compliance with this rule, or the effect of varying doses of phenylbutazone on the blood levels of phenylbutazone likely to be found after different dosage schedules. On the other hand, such information as is available in this area has been reviewed by Tobin et al. (1986), and allows some approximate judgements to be made in the area.

ADVERSE REACTIONS

As suggested earlier, adverse reactions to phenylbutazone are not uncommon, and toxicity to this drug can readily be produced. This came as a considerable surprise to most equine clinicians, since it had long been considered that phenylbutazone was virtually non-toxic in the horse. However, it is now clear that early workers underestimated the toxicity potential of phenylbutazone. When given at high dose levels, even for short periods, cumulation, and hence toxic effects, can rapidly and readily occur. Toxicity appears as inappetence, melena, depression, mouth ulcers, diarrhea and possibly abdominal edema. If the drug is being administered in food, the condition tends to be self-limiting, since the animal will refuse to eat after a few days. If dosing is maintained, however, more serious toxicity and death may occur. The sequence of events usually involves gastrointestinal ulceration and a resulting loss of plasma leading to hypovolemic shock. If the animals' access to water is restricted, renal lesions may also occur. Alternatively, the cause of death may be related to colic, and the intestinal changes may lead to septic (endotoxic) shock. If the drug is withdrawn at the first signs of toxicity, the chances of complete recovery are good. However, signs of toxicity can persist for weeks after the drug has been withdrawn (Snow et al., 1981).

A major difficulty in evaluating reports of toxicity induced experimentally by phenylbutazone is that plasma levels of phenylbutazone and oxyphenbutazone producing these effects are unknown. Because of uncertainties about the ability of phenylbutazone to accumulate under the conditions of these experiments, the plasma levels producing these toxic responses and their relationship to the levels likely to be found in horses on therapeutic regimens of the drug are not known. Careful evaluation of the pharmacokinetics of phenylbutazone under conditions where cumulation and

toxicity occurs is needed. Also, the contribution that the dose-dependent pharmacokinetics of phenylbutazone makes to toxicity should be evaluated. Even now, however, it is possible to speculate that the dependence of phenylbutazone half-life on hepatic metabolism, the possibility that therapeutic doses saturate the enzyme system involved in metabolism, and the further possibility that phenylbutazone is hepatotoxic could lead to a cycle of cumulation and toxicity.

While phenylbutazone is a drug with a narrow therapeutic index, it should be noted that none of the toxicity studies has led to suggestions that the doses of phenylbutazone recommended for use in North American need to be changed. In the Great Britain, however, the loading doses of this drug recommended by one manufacturer were reduced from 4.4 mg/kg twice daily to once daily for 4 days (Taylor et al., 1983). Similarly, the American Association of Equine Practitioners has recommended that the dose should occur not more than 24 h before post time. Under these conditions, and with due precautions to ensure proper hydration, phenylbutazone should continue to be a safe and effective medication in the horse. Clinical experience over many years certainly suggests that moderate doses can be given over prolonged periods without inducing clinically detectable side-effects.

FLUNIXIN

Flunixin (Banamine^{R}; Schering Corporation, Kenilworth, NJ) is another member of the NSAID family that appears to be slightly more potent than phenylbutazone (Tobin, 1979). It is well absorbed after oral administration, and is rapidly distributed in the horse. This rapid distribution phase results in a relatively short plasma half-life for flunixin in the horse, and by about eight hours after dosing the drug is difficult to detect in blood. On the other hand, more recent work suggests that the drug may have a very prolonged terminal plasma half-life in the

horse and that its clearance in urine can be slow (Chay et al., 1982). However, as a practical matter most of the drug should have cleared the urine of the horse by about 48 hours after the last dose, so this appears to be a reasonable clearance time of this drug in the horse. While the drug can be detected beyond this time, the likelihood of a pharmacological effect at this time is small and the amounts of drug present in the urine sample are also likely to be small.

Flunixin has a reputation of being especially useful in the treatment of colics, with the response to administration of this drug being very prompt, but lasting for about six hours. Because of the very rapid onset of the action of flunixin and its relatively short action, the pharmacological basis for the actions of this drug in the treatment of colic are not clear. This use of the drug appears to be well established, and flunixin is that NSAID of choice for the treatment of colics.

Unlike phenylbutazone, flunixin does not appear to accumulate in the horse and "clearance times" after sequential doses of flunixin are not significantly different from the clearance times for this drug after single doses of this drug.

NAPROXEN

Naproxen (Equiproxen^{R}; Diamond Laboratories, Des Moines, IA) is another NSAID drug with pharmacological actions similar to phenylbutazone (Tobin, 1979). It is recommended for the relief of pain, inflammation and lameness associated with "tying up" and soft tissue disease of the horse. The most provocative work with naproxen has been that of Hamm (1978) who evaluated the effects of continuous administration of naproxen to fifty yearling quarterhorse colts during training. As reported earlier, the horses treated with naproxen raced significantly more often than control horses, and the overall frequency of musculoskeletal injuries was dramatically reduced, by

four-fold during training and by thirty-fold during racing, suggesting a case for the benefits of anti-inflammatory medication in young horses in training.

Naproxen is relatively rapidly cleared from the plasma of horse and is recommended for administration twice a day. It thus is unlikely to accumulate in the horse, so the clearance time after a single dose should not be significantly different from that after multiple doses. On the other hand, naproxen is a relatively easy drug to detect in blood and urine, and at least sixty hours should be allowed for this drug to clear the urine of horses.

MECLOFENAMIC ACID

Meclofenamic acid (Arquel^{R}; Parke-Davis and Company, Detroit, MI) is another member of the NSAID group of drugs (Tobin, 1979). It is unusual among NSAID drugs in that its onset of action takes about one and a half to three days to develop. In contrast with this slow development of the pharmacological effect of the drug its plasma levels peak rapidly, within one to four hours after a single dose, and then decline to clear the plasma after about twenty four hours. Because meclofenamic acid essentially clears the plasma after twenty four hours there is little tendency for meclofenamic acid to accumulate in the plasma of a normal horse.

After a normal dosage schedule of meclofenamic acid, this drug is reportedly detectable in urine for up to 96 hours, although the levels are very low up to 48 hours after dosing. As with phenylbutazone, toxicity to meclofenamic acid appears at high dose levels of this drug, and include mouth ulcers, loss of appetite, edema and loss of weight. However, if as with phenylbutazone the dosage rate is kept low and the dosage period is not unduly extended meclofenamic acid is a safe drug for use in the horse.

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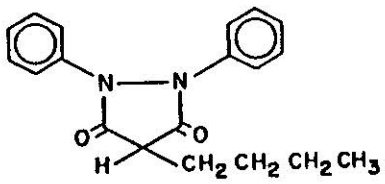
Figure 1. Structure and physical characteristics of phenylbutazone. Reproduced with permission from J. Vet. Pharmacol. Therap.

Figure 2. Inflammatory mediators formed from arachidonic acid. Code: PG, prostaglandin; TX, thromboxane; LT, leukotriene; SRS-A, slow-reacting substance of anaphylaxis; HPETE, hydroperoxyeicosatetraenoic acid: HETE, hydroxyeicosatetraenoic acid. Reproduced with permission from J. Vet. Pharmacol. Therap.

Figure 3. Absence of analgesic effect of i.v. phenylbutazone (PBZ) on hoof withdrawal reflex latency. Values represent mean post-treatment latency (± S.E.M.) expressed as a percent of the mean pre-treatment (control) latency. Pre-saline = 6.9 ± 0.6 s. Pre-PBZ latency = 7.1 ± 0.5 s. n = 8. Reproduced with permission from Europ. J. Pharmacol.

Figure 4. Nerve blocking action of mepivacaine (2%) on hoof withdrawal reflex latency. Values are the mean post-treatment latencies (± S.E.M.) expressed as a percent of the mean pretreatment (control) latency. Pre-saline = 8.4 ± 0.6 s. Pre-mepivacaine latency = 6.3 ± 0.4 s. n = 6. Reproduced with permission from Europ. J. Pharmacol.



4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione

Solubility

Phosphate buffer pH 7.0 (20°)	1.88 g/l
Methylene chloride	>1.00 g/l

Partition coefficient

$\left[\frac{C_{organic}}{C_{aqueous}}\right]$

Methylene chloride / buffer pH 7.3	476
n-Octanol / buffer pH 7.4	5
Peanut oil / buffer pH 7.4	2.2

Acidity

pKa (water)	4.5

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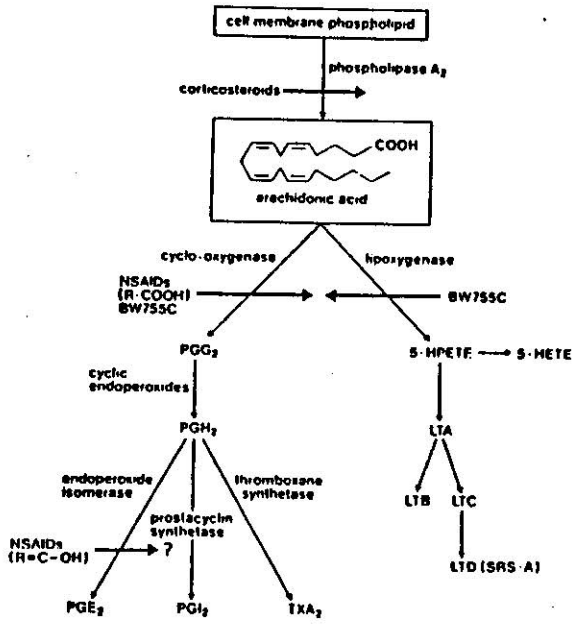

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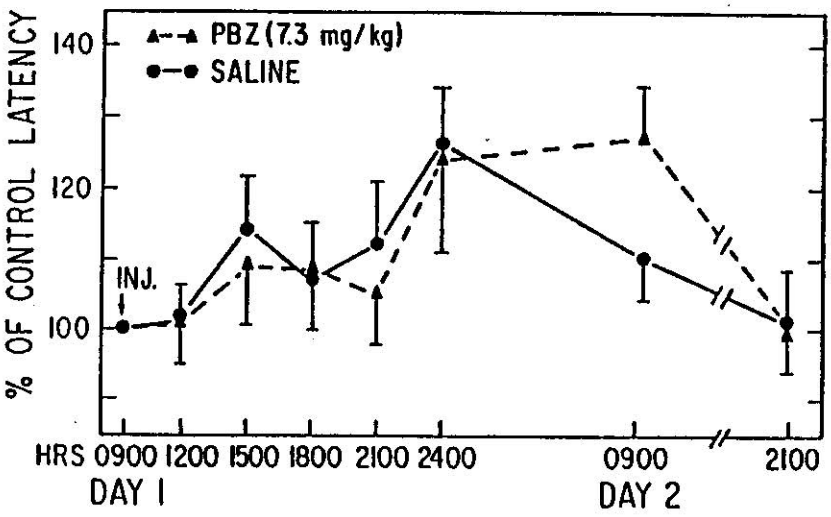

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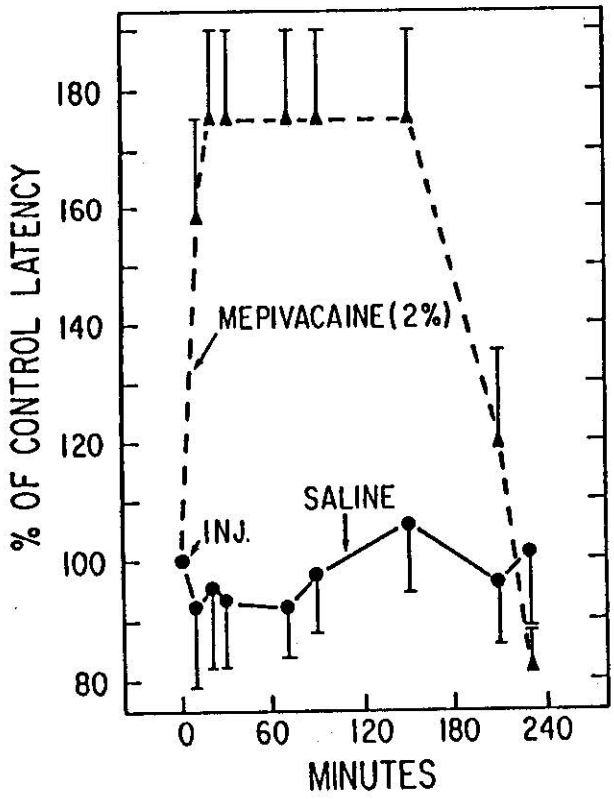

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