Pharmacology

Non Reviewed

MEDICATION CONTROL : RULES

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SUMMARY

The simplest medication rule is a "no detectable level" rule. This rule is used in much of Europe and North America. The principal problem with this rule is that it is virtually impossible to give any guidance to horsemen as to when they should cease drug administration. Part of the reason for this is that the analyst can change the rule at will, simply by changing his detection method.

A much more equitable rule is one that specifies a blood or urinary tolerance for a drug. When a tolerance is specified, changing the test method is of no significance, and guidelines can be given to horsemen to help them comply with the rule. The National Association of State Racing Chemists' tolerance for phenylbutazone is a classic example of such a rule.

Both of these rules have the advantage that the event which defines the violation is objective and independently verifiable. In each case, the drug can be detected or quantitated by an independent analyst. *Independent confirmation* removes all doubt as to the scientific basis of the regulatory action.

Time rules specify times prior to post during which drugs cannot be administered. While such rules read well and are easy to write, they are troublesome to enforce. This is because enforcement of a time rule depends not on a measured blood or urinary drug level, but rather on an analyst's opinion as to when the drug was administered. This opinion will always have a probability of error, which may be greater, for example, than the number of horses that the analyst tests per year. Under these circumstances, the horsemen's testimony may be correct, and the analyst's opinion incorrect, in a significant proportion of cases. No *objective, independent* check of the analyst's opinion is possible, and neither are contrary opinions independently verifiable. Such a regulatory process is unsatisfactory and may undermine the credibility of the analyst.

Because of the technical difficulty and expense of medication control, the strategy of no control for some medications is an option which requires careful evaluation.

INTRODUCTION

There are four basic types of medication rules in use in the world today. The simplest is the "no detectable level" rule, which specifies that no trace of any drug shall be found in any body fluid. A major jurisdiction using such a rule is England. In England, this rule comes with virtually no guidelines as to how horsemen may ensure that no traces of medication are detected.

No detectable level rules also operate in Canada and Australia, with the difference that these jurisdictions make an effort to help the horsemen with "withdrawal periods" for commonly used drugs. We will take some time to study the Canadian approach to this problem, as the Canadian approach highlights the problems with this type of rule.

The second type of rule, which is just beginning to be used, is the "tolerance level" type rule. The classic example of this rule is the NASRC blood level tolerance for

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phenylbutazone of 2µg/ml in blood*. While not without its problems, this type of rule is the most equitable approach to the problem of medication control in horses.

The third rule is the time rule, which states that drugs shall not be administered within a certain period before post. While such rules are easy to write and understand, they are difficult to apply for technical reasons. Perhaps for this reason, such rules are not widely used.

The fourth type of rule is no rule at all. Virtually all American jurisdictions have agents whose use they disregard and are therefore unregulated. Given the expense and technical difficulty of medication control this is a regulatory option that should not be dismissed out of hand.

The No Detectable Level Rule

A no detectable level rules states that no trace of any drug or drug metabolite shall be found in the blood or urine of a horse. Simple confirmation of the presence of a drug is evidence that an offense has been committed. This rule disregards the fact that below a certain level, drugs have no effect on the performance of a horse. In approach, this rule is rather like the approach to carcinogens in food, which holds that there shall be no detectable trace of any carcinogen in foodstuffs. While a no detectable level rule is a very rigorous rule, it is one that seems to work well in England. To comply with this rule, the English authorities suggest that no drug be given to a horse within ten days of post time, which "guidelines" should cover "all but the most slowly eliminated drugs." While this is an extremely strict rule, and is indeed the most rigorous rule I know of, it appears to work well in England.

This rule is forensically "clean." If an analyst detects a drug in a blood or urine sample, he can send a referee sample to another lab, and the medication he reported can be independently confirmed. The analyst therefore testifies to a scientific fact that can be independently confirmed. The rule states that there shall be no detectable amount of drug in the blood or urine sample, so the rule has clearly been broken.

There are two problems with this rule. Because drugs are given at such different doses (one-million fold) and are excreted at such different rates, it is very difficult to make estimates as to when administration of the drug should cease so that the level in the body fluid will be below the level detectable in the analyst's tests. For this reason, it can be very difficult for a horseman or veterinarian to make any kind of informed judgement as to at what time prior to post a drug should be withdrawn.

The second problem with this rule is that if the analyst changes his method, then in effect the rule has been changed. The analyst can do this at any time. However, since there is no relationship between "traces" of drug and its pharmacological effect, the sensitivity of the test is unlikely to be in any way related to the possible performance effects of the drug. If a better test is introduced, there may well be a transient increase in the number of positives, even though the rule is in fact being applied just as rigorously (with regard to possible effects on performance) as previously.

In effect, the analyst arbitrarily decides how rigorous the rule will be when he selects the test. This is not a desirable state of affairs, but is inevitable under this type rule.

This ability of the analyst to arbitrarily change the rule is a potential defense in the case of positives called under this type of rule. In particular, if the drug in question is a "soft" medication, such as one of the phenylbutazone analogs, there already exists both precedent and rationale for the presence of traces of these drugs in blood or urine. Under these circumstances, one could argue that there should be a similar residue level for the drug in question, and that the analyst should not have the power to arbitrarily set the actionable level, as he does under a no detectable level rule. However, the value of this defense is much less if the drug in question is a hard or illegal drug, whose presence in the horse in the first place is suspect.

A number of other jurisdictions have rules that are qualitatively similar to the "English rule," with the exception that they offer more detailed guidance as to the times before racing that specific medications should be withdrawn. Examples of such rules are the Australian and Canadian rules. Because of the geographic closeness of Canada, and the amount of material that they have presented on their rule, we will examine the Canadian approach to the problem of medication control.

The Canadian Approach

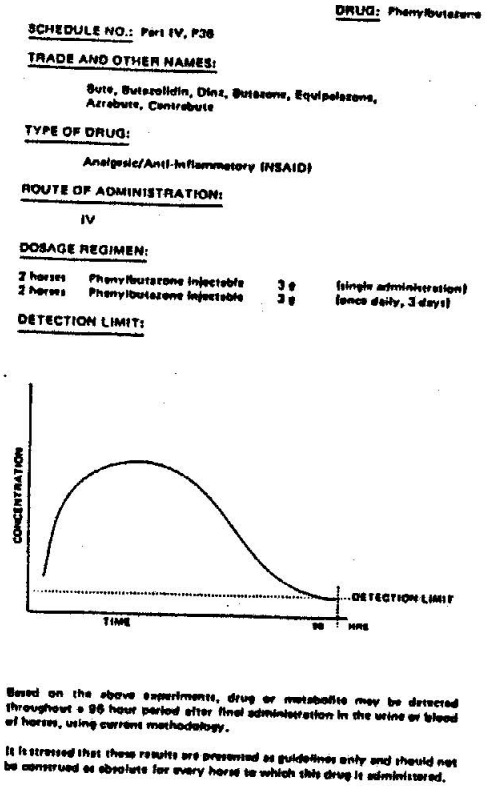
The basic difference between the English and the Canadian rule is that the Canadian authorities have instituted a research program to "determine" the detection times for about forty different drugs in horses. As an example of the approach of the Canadian authorities, we show, in Figure 1, some of the data that the Canadian authorities have published on phenylbutazone.

To obtain this information, two horses each were dosed intravenously with phenylbutazone, either one single dose or with daily doses for three days. Then they looked for this drug in either blood or urine, and noted the period for which the drug could be detected. Although the published curves look very professional, they are, in fact, of no value as a scientific study, and misleading to most casual observers.

In the first place, the curves published are in error. This is because the same kinetic curve is not likely to be found after a single dose, and after three daily doses of a drug. In this particular figure, the curve represents the author's imagined level of drug, and is not to be taken seriously.

The test medium is not described, and there is no way of knowing whether it is blood, urine, or saliva. No concentration units are given, and the methodology is noted as "current," with the clear implication that current methodology may change. Finally, there is a very explicit disclaimer at the bottom of the page in which "It is stressed that these results are presented as guidelines only, and

* More recently, this suggested tolerance has been changed to 5µg/ml.



DRUG: Phenylbutazone

SCHEDULE NO.: Part IV, P36

TRADE AND OTHER NAMES:

Bute, Butazolidin, Dinz, Butazone, Equipalazone, Azrobute, Contrabute

TYPE OF DRUG:

Analgesic/Anti-Inflammatory (NSAID)

ROUTE OF ADMINISTRATION:

IV

DOSAGE REGIMEN:

2 horses	Phenylbutazone injectable	3 g	(single administration)
2 horses	Phenylbutazone injectable	3 g	(once daily, 3 days)

DETECTION LIMIT:

Based on the above experiments, drug or metabolite may be detected throughout a 96 hour period after final administration in the urine or blood of horses, using current methodology.

It is stressed that these results are presented as guidelines only and should not be construed as absolute for every horse to which this drug is administered.

should not be construed as absolute for every horse to which the drug is administered." In the language of the street, this says "In two horses, we found phenylbutazone for 96 hours, but you are on your own." This is fractionally better than the English approach, but not by much.

So how useful is the Canadian information? Well, let me first say that, outside of our own work in Kentucky, this is the most elaborate effort in this area in the world, and it is the only one in which an attempt has been made to publish the data. However, the guidelines only show that one must *not* give the drug within the suggested period. The question which remains is the critical one, i.e., how far does one have to go outside of 96 hours to be "safe," or conversely, how "safe" is one if one goes 24 or 48 extra hours outside of the 96 hour period? No information is available to answer these questions, and with the type of approach presented by the Canadians, these questions can never be answered. The Canadian data, however, points clearly to two problems that have to be answered, one being the "current methodology" problem, and the other being the horse-to-horse variability problem. The answer to both of these problems is a quantitative rule.

Quantitative Rules

If one sets a quantitative level, then methodology does not matter. The tolerance for phenylbutazone under the NASRC rule is 2µg/ml, period. The analyst can change his methodology, but the level at which a violation occurs does not change. The way out of the methodology problem is to have a quantitative limit for the drug, preferably in plasma, where there are fewer confounding variables than in urine.

The second problem that is answered by quantitation is the question of how safe is one if one follows a certain dosing schedule. This is because if there is a set level, one can dose horses as outlined in the last article, measure the drug levels found in about fifty of them and from this data one can arrive at reasonable estimates of the probability of having a horse go over the tolerance level. This kind of probability information also brings home to all concerned in medication regulation the high level of uncertainty about what kind of blood or urine levels will be found in large numbers of horses after dosing with a given amount of drug.

This type of rule is also forensically clean. The analyst and the horseman know what the tolerance for the drug is in advance. The analyst detects the drug in the sample, and quantitates it. He can detect with high accuracy, and quantitate with an accuracy of about ± 30%. If he has any sense, he will not call a positive unless his assay gives a reading of 40% more than the tolerance level. If the horseman so wishes, he can have the sample sent to another analyst, who will be able to confirm the analytical findings. The analyst testifies only to objective facts that can be independently confirmed. The analyst and the authority are clean, and the blame lies with the horse or the horseman. Further, there are no conceptual grounds on which the procedure can be attacked, as there are with "no detectable level" rules and time rules.

With this type of rule it is usual to give the horsemen feedback as to the quantitative levels of drugs being found in their horse. If this is done, experience in Illinois suggest that the horsemen move rapidly to ensure that blood levels in their horses are kept below the actionable level, and compliance with the rule is good. In addition, because of the statistical nature of the probability of an "overage," trainers with large numbers of horses are allowed more "overages" before administrative action is taken, than trainers with small numbers of horses.

Time Rules

The third type of rule that is used in this country is time rule. In this rule, the period before a race during which certain drugs cannot be administered is stipulated. This rule is easy to write, is easy to read, and is a "clean" rule on paper. However, from a scientific and forensic standpoint, it is a very troublesome rule.

The classic example of a time rule is the New York rule. Under this rule, for example, administration of phenylbutazone is prohibited within 48 hours of post time, pentazocine (Talwin) within 72 hours of post time, and procaine, in any form, within 7 days of post time. While this is an easy rule for horsemen and laymen to follow, it is not an easy rule to enforce.

To the best of my knowledge, enforcement of this rule is based on scientific data that is broadly similar to the Canadian data, i.e., experiments in small numbers of horses (<10), with the "times" derived from these data. However, exactly the same questions as arose with the Canadian data arise with the time rules, i.e., how soon after the times obtained on small numbers of horses is one "safe," and how "safe" is one if one gives the drug at a certain time. The answers to these questios are not at all clear, but they have major implications for the enforcement of time rules, and render time rules by far the least satisfactory approach to the problem of medication control.

For the authority to enforce a time rule, its analyst will have to swear that he can tell the time that the drug was administered to the horse with *no* margin of error. If he cannot do this, he cannot enforce the rule. The authority's expert, therefore, will be under great pressure to overlook the uncertainty in his tests and make a flat statement of time of administration.

Now, let us imagine a hypothetical situation in which all the horsemen in a jurisdiction are obeying time rules that have been established in small numbers of horses, such as those reported in the Canadian studies. If they all give a drug, let us say phenylbutazone, at 60 hours prior to post, the probability is that a small proportion of these horses will show positive in the analyst's tests. This is because the analyst in his studies only tested ten or fewer horses, but there are literally thousands of horsemen out there giving phenylbutazone, and all are obeying the rule. Due to the way that horses can spread out blood and urinary levels of drugs, some of these horses will inevitably show "positive". In post-race samples, the analyst sees the high concentration "tail" of the log-normal distribution, and based on his six-horse laboratory experiment, he calls a "positive."

When it comes to the hearing, the analyst will have to swear that the drug was given within 48 hours. He will do his best to downplay the probability of error in his estimate, or he may deny it or ignore it altogether. In actual fact, however, the probability of error in his estimate may be substantial, and, for example, be large compared with the number of horses that he tests in a year. Under these conditions, the horseman, who well knows the true time of drug administration, knows that the analyst is in error, and will likely formulate an opinion as to his character and ability. The horseman, however, is in the unfortunate poisiton of being totally unable to defend himself.

The horseman cannot defend himself because the evidence of his infraction is not objective and independently verifiable. Rather, the evidence on which he will be convicted is an opinion of the analyst as to when the drug was administered. To defend himself, the best that the horsemen can do is produce another expert, who will offer a contrary, and possibly more correct opinion. Unfortunately no objective independent verification of which opinion is correct is possible. The hearing becomes a contest of opinions. As a general rule, authorities tend to support their own analyst in matters of opinion. Indeed, as a matter of policy, they are forced to, for to do otherwise would be to deny their own competence as regulators.

This is a very unsatisfactory state of affairs, and if the regulated individual knows that in fact the analyst is wrong, he will have good reason to question the analyst, and also the authority who employs the analyst If the situation repeats itself, the credibility of the analyst and his authority can be severely undermined, and lead to adversary situations between the regulator and the regulated. Rules such as the previous two, where the evidence of an infraction is factual, objective and independently verifiable, are much more satisfactory rules than time rules.

In summary, although a time rule looks good on paper, it is subject to scientific error and administrative rigidity. The probability of scientific error is finite, at this time unknown for most drugs, but is most assuredly not small. The analyst, by virtue of his role as a regulator, is forced to downplay this problem, and "talk up" the accuracy of his tests. He will likely present a strong *opinion* as to the accuracy of his estimate.

Contrary opinions are the only possible defense, and will be heard by an authority whose creatures the rules and analysts are. No objective independent evidence of innocence can ever be obtained. For these two reasons, time rules are forensically troublesome, and are less than satisfactory solutions to the problem of equine medication control.

No Rule

The fourth and last type is no rule at all. While this rule might seem to be a dereliction of duty on the part of a regulator, it is, in fact, a very real option that should not dismissed out of hand. This is because most jurisdictions have agents that are technically medications or foreign substances that appear in their horse urines, but that they do not in fact call, or only rarely call. The best known such example is DMSO, a topical anti-inflammatory and aid to drug penetration, which the Vet Chemists Committee of the NASRC has suggested should not be considered an illegal medication when used topically.

When the alternative to the calling of positives for an agent is to tolerate the presence of small amounts of this agent in the blood or urine of horses, and when the regulatory strategies are likely to be cumbersome and expensive, the best solution to this problem may simply be to permit use of the substance without regulation. This is a regulatory option that requires some courage on the part of the regulators, but it is an option which under some circumstances may be by far the best solution to the problem.

Combined Rules

There is no reason that these four different rule types cannot be used in combination. The classic example of this is the State of Illinois, where at least three of these rule types are in use. In Illinois, the basic rule type is "no detectable level of any substance foreign to the natural horse," the most stringent possible "no detectable level"

rule. However, there is a specific exclusion for phenylbutazone, at the recommended limit established by the NASRC of 2μg/ml. Beyond this, the use of furosemide is permitted at the dose of 250 mg, administered not less than 4 hours prior to post time. These are the recommendations of the American Association of Equine Practitioners for furosemide. In general, the Illinois rule, while strict, is apparently thoughtfully and equitably administered, and appears to work well.