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'Detection times' and 'clearance times' for drugs in horses and other animals: a reappraisal

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Review of the veterinary literature shows that many workers in this area believe that after drug injection, the concentration of drug in the animal never reaches zero. For example, a recent text of veterinary pharmacology (Jones, Booth & McDonald, 1977) states that 'In essence, depletion of a drug from the tissues of an animal never reaches a zero concentration or zero tolerance level'. This opinion arose because animals eliminate most drugs in an exponential manner following simple first order kinetics (Tobin, 1981; Baggot, 1977). Such elimination curves are usually plotted semi-logarithmically, as declining drug concentrations against time (Fig. 1). Inspection of such graphs may lead to the conclusion that drug elimination can continue indefinitely since theoretically at least (Tobin, 1978; Pugh, 1978; Sanford, 1978; Blake, 1979) drug concentrations can continue to decline indefinitely. While this conclusion is mathematically correct and has been drawn by many (including Tobin, 1978), it is for all practical purposes erroneous.

The error of this conclusion becomes apparent if one expresses the data as drug molecules/animal (Fig. 1). As an hypothetical example, let us assume that 6×10^{21} molecules of phenylbutazone* with a half-life of 7.223 h are injected into a horse. Figure 1 shows that at this half-life the horse eliminates 90% of 1 log unit of the drug dose in exactly 1 day. If this rate of excretion continues, by 21 days after dosing the horse will be eliminating the last drug molecules. Drug clearance occurs when the last drug molecule is excreted and the drug concentration in the horse abruptly falls to zero.† While the concept of a fraction of a drug molecule/horse is mathematically correct, it does not occur in practice.

The number of half-lives which must elapse before the last drug molecule is available to

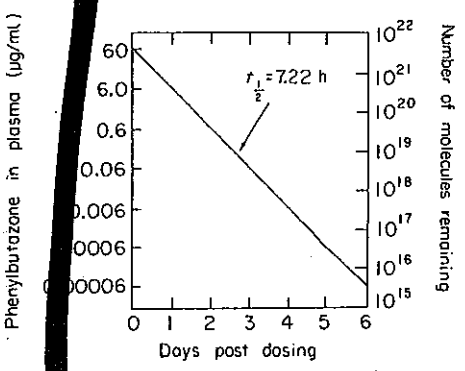

FIG. 1. Elimination of a hypothetical dose of phenylbutazone by a horse. A dose of 3 g phenylbutazone/450 kg horse means that about 6×10^{21} molecules of phenylbutazone are injected into the horse. This dose will give an initial blood level of approximately 60 µg/ml. If the drug is cleared with a $t_{\frac{1}{2}}$ of 7.22 h, 90% of the administered dose will be eliminated every 24 h. By extrapolation, elimination of the last drug molecules will occur at about 21 days after dosing assuming that each drug molecule has the same probability of being eliminated by the horse, whether it is the first or last molecule eliminated.

*A commonly used clinical dose is approximately 3 g/450 kg.

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†This outcome requires only that elimination of the drug continue to follow first order kinetics and the same rate constant. Good experimental and theoretical grounds exist to support this suggestion. The method is independent of any conceptual pharmacokinetic compartments for interpreting the actual rate of decline in drug levels.

be excreted depends only on the number of drug molecules injected (Fig. 2). With highly potent drugs, for example etorphine or hyaluronic acid, about 10^{16} molecules are injected and the drug clears to one molecule/horse in about fifty-five half-lives. For less potent drugs, for example phenylbutazone, between 10^{20} and 10^{22} molecules must be injected, thus requiring approximately seventy half-lives for clearance of the drug to one remaining molecule (Fig. 2). For drugs of intermediate potency, the number of half-lives required for clearance is intermediate. Therefore, the variation in the number of half-lives required to excrete any drug is relatively small, and it has been suggested as a general rule that it takes about sixty-six half-lives for any drug to be 'cleared' to one molecule/horse (Tobin, 1981).

The time taken to clear the last drug molecule also depends on the half-life of the drug. Given a population of horses or other animals containing one drug molecule, 90% of them will clear that molecule within 3.3 half-lives, and more than 99% within seven half-lives. Therefore, within about seventy-seven half-lives, 99% of all horses given, for example phenylbutazone, will be drug free. These calculations show that the hypothesis that drug molecules never clear from horses or other animals is wrong for all practical purposes, and that the great majority of horses will clear all administered drug molecules within seventy-seven half-lives or less.

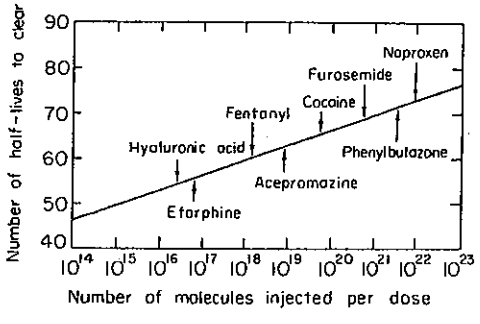

FIG. 2. Relationship between the number of molecules administered and number of half-lives to clear one remaining drug molecule. This relationship is expressed by the equation: (ln no. of molecules injected)/(0.693) = half-lives to clear. Thus, if the number of molecules injected is relatively large (i.e. naproxen, phenylbutazone) more than seventy half-lives are needed to clear the drug to one molecule/horse. The arrows show the number of drug molecules injected with a typical dose of each drug and the number of half-lives taken by each dose to 'clear' to one drug molecule/horse.

While the number of half-lives taken by a drug to clear a horse is relatively constant, the actual time taken by different drugs is highly variable. The half-lives for drugs in horses vary about 100-fold, from approximately 1 h (amphetamine and cocaine) to approximately 20 h (caffeine and procaine) to the apparently very long half-lives of pemoline (150 h) and probably reserpine. Therefore, the actual time taken for drugs to clear a horse can vary from about 2–10 days for rapidly excreted drugs, to 30–66 days for phenylbutazone and to 494 days for a dose of pemoline. Similarly, reserpine, which has been reported to have an 11-day half-life in man, would take almost 2 years to clear after a single dose (Table I).

Assuming that current analytical techniques will begin to fail to detect drugs at about 10^{17} molecules/horse, some interesting conclusions can be drawn with reference to performance horse medication. In general, relatively large numbers of molecules (10^{21}) of the acidic drugs have to be injected, and clearance is relatively slow. For these drugs detection over a relatively prolonged period of time is possible, and blood or, less satisfactorily, urinary level limits can be set. Alternatively, with the basic central nervous system stimulants, the number of molecules injected is smaller and clearance may be relatively rapid. The period is short when these drugs are likely to be detectable in plasma or urine. Finally, for drugs which are administered at doses of approximately 10^{17} molecules or less, simple detection and identification remains a challenge.

Analysts, veterinarians and administrators often refer to the period when a drug can be detected in a horse as a *clearance time*. We believe this is a confusing way to describe an event which may be largely dependent on the analyst's methodology. We propose that the phrase *detection time* be applied to the period after dosing when a drug can be detected. The term *clearance time* can then be applied to the actual time taken by the drug to clear the horse. The advantage of this nomenclature is that it highlights the role of the analyst's methods in determining how long the drug may be detected and emphasizes that 'clearance' continues quite independently of the 'detectability' of the drug.

TABLE I. Lack of relationship between number of half-lives to clear and the estimated time for drugs to clear 99% of horses

Drug	Molecular weight	Dose	Molecules/dose	Number of half-lives to clear 99% of horses	Half-life (h)	Estimated *clearance time* (days)
Etorphine	411.52	0.045 mg	6.58×10^{16}	63	–	–
Fentanyl	336.46	1 mg	1.79×10^{18}	68	21 (Urine)	60
Furosemide	330.77	250 mg	4.55×10^{20}	76	7.6 (Urine)	24
Methylphenidate	233.30	400 mg	1.03×10^{21}	77	3.4 (Plasma)	11
Naproxen	230.26	4 g	1.05×10^{22}	80	–	–
Pentazocine	285.44	500 mg	1.05×10^{21}	77	16 (Urine)	51
Phenylbutazone	308.37	2 g	3.90×10^{21}	79	7–20 (Urine)	24–66
Reserpine*	608.70	2.5 mg	2.47×10^{18}	68	264* (Plasma)	748
Procaine†	236.30	2.4 g	6.11×10^{21}	79	24 (Urine)	79
Caffeine	194.19	1.8 g	5.58×10^{21}	79	17 (Urine)	56
Meclofenamic acid	296.15	4 g	8.13×10^{21}	80	6 (Plasma)	20
Cocaine	303.35	50 mg	9.90×10^{19}	73	0.75 (Plasma)	2
Amphetamine	135.20	150 mg	6.68×10^{20}	76	1.4 (Plasma)	5
Flunixin meglumine	296	500 mg	1.02×10^{21}	77	4 (Urine)	13
Pemoline	176.17	1.125 g	3.84×10^{21}	79	150 (Plasma)	494
Morphine	285.33	45 mg	9.49×10^{19}	73	5.98 (Urine)	18

*Extrapolated from human $t_{1/2}$.
†As procaine penicillin.
The number of drug molecules injected per dose and the number of half-lives to clearance are presented for a selection of drugs commonly used in the horse. From this data and published blood or urinary half-lives for these drugs in the horse, we estimate the times taken for these drugs to actually 'clear' 99% of a population of horses. Dose data and half-lives for drugs in horses are taken from Baggot (1977) and Tobin (1981).

In summary, therefore, although animals excrete most drugs exponentially the concept that this process continues indefinitely is incorrect. About 99% of a given population of horses will 'clear' most drugs within less than seventy-seven half-lives, the actual number of half-lives is dependent on the number of drug molecules injected into the horse. The *time* to 'clear' is determined primarily by the half-life of the drug and in the horse can vary from as little as 4 days (amphetamine) to 494 days (pemoline). Most drugs appear to clear horses within approximately 20–60 days after dosing.

Given the current status of the analytical art, all drugs continue to clear long after they are undetectable. We propose that the period when a drug may be detected be called the *detection time*, with the term *clearance time* reserved for the period taken for the drug to clear the horse.

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