Reports

Toxicity, the Therapeutic Index, and the Ranking of Drugs

Abstract. *The therapeutic index is often used to rank the net effectiveness of drugs and to provide a guide for choosing the best among several drugs. This can be a misleading guide since we show that drugs with the same therapeutic index can have unequal "worth." A substitute ranking measure for the therapeutic index is proposed that would be based on minimizing the losses from the failure to cure plus the losses due to toxicity. This measure would specify a "best" dose over a wide range of conditions, which the therapeutic index does not do. An example is given in which the minimum loss approach produces a ranking of drugs different from that produced by the therapeutic index. In this example the different rankings hold, with minor shifts, over a wide range.*

Food and Drug Administration regulations (*1*) require a balancing of the activity of a drug against its toxic side-effects. This clearly implies relative ranking of drugs on this balance. The most commonly used ranking metameter is the therapeutic index (TI). The drug with the highest therapeutic index is assumed to be "best," the relative worth declining with the index. In this report we raise the question of whether the therapeutic index is the proper measure for ranking; by way of an answer, we now propose a substitute.

Ehrlich (*2*) defined the therapeutic index as the ratio of the highest dose at and below which there was no toxicity, to the lowest dose at and above which there were all "cures." Behrens (*3*) showed that under this definition, the therapeutic index must become smaller as the experiment size increases. Recent workers have attempted to find a stable measure that would be independent of experiment size. We follow some of them (*4*) in defining therapeutic index as the ratio of the dose at which there is no more than 5-percent toxicity (TO5) to the dose at which there are at least 95-percent "cures" (A95). The TO5 is obtained from the dose-response curve for toxicity and A95 from the dose-response curve for activity for the particular drug. A material with a high therapeutic index would have a wide spread between the A95 and TO5 doses and is thus assumed to be safer to use than one with a lower index.

In part, the considerable intuitive appeal of the therapeutic index arises from the awareness that the A95 and TO5 doses are rarely determined with accuracy. The physician must have a safety factor, and he feels that the higher the therapeutic index, the greater the safety factor. It is often assumed that a drug with a therapeutic index of less than 1 is not usable. Thus an attempt to deal with the safety problem in the face of incomplete information is part of the appeal of the therapeutic index. It would appear wise to investigate the utility of this measure where one has complete information. If complete knowledge about a material leads to a measure other than that of the therapeutic index, then there are implications about the amount of experimental work that should be done (and of how much data one needs before abandoning the therapeutic index).

One additional difficulty inherent in the therapeutic index is that it does not tell at what dose the drug should be administered. It is usually assumed that almost any dose less than the "toxic" dose (TO5) and greater than the "active" dose (A95) is suitable. A procedure which yields a single "best" dose would be more desirable.

In regard to the minimum loss index (*5*), "loss" L may be defined as

$$L = (1 - q_1) + \lambda q_2 \qquad (1)$$

where $(1 - q_1)$ is the loss due to failure to cure (percentage of persons or animals who were not cured), q_2 is the loss due to toxicity (percentage of persons or animals who showed toxic responses), and λ is a weighting factor giving the relative importance of toxicity compared to the failure to cure.

Our purpose is to find that dose of drug which will give minimum loss. In turn, when we wish to rate drugs in relative order, we will rate them in terms of this loss: the smaller the loss, the better the drug.

Let us assume that a well-planned, infinitely large experiment has been conducted. We would then know the exact dose-response curves for activity and toxicity. Thus we would know TO5 and A95 and the slopes of the dose-response curves, b_T and b_A without error.

Under log-normality assumptions for dose-response models, $(1 - q_1)$ is the area under the upper tail of a normal distribution with log mean μ_A and log variance σ_A^2 where $\sigma_A = 1/b_A$, and $\mu_A = A95 - 1.645\ \sigma_A$, and q_2 is the area under the lower tail of a normal distribution with log mean μ_T and log variance σ_T^2 where $\sigma_T = 1/b_T$ and $\mu_T =$

Table 1. Relative rankings of five drugs by therapeutic index (TI) and by minimum loss (ML) ($\lambda = 1$).

Drug	TI*	Doses† TO5 (arithmetic units)	Slopes‡		"Best" dose		Rank		Relative§ worth	
			Activity	Toxicity	Arithmetic units	Relative loss	TI	ML	TI	ML
A	4	4	2	8	2.70	.0037	1	2	100	59
B	2	2	8	8	1.41	.0022	2	1	50	100
C	2	2	2	8	1.52	.0135	2	3	50	16
D	2/3	2/3	8	8	0.82	.1734	3	5	17	1.3
E	2/3	2/3	2	8	0.60	.0685	3	4	17	3.2

*Therapeutic index computed as ratio of the arithmetic doses TO5/A95. †All A95 doses set at one arithmetic unit. Thus log A95 = 0. ‡Normal deviates per tenfold dilution. §Relative to the first-ranked drug valued at 100.

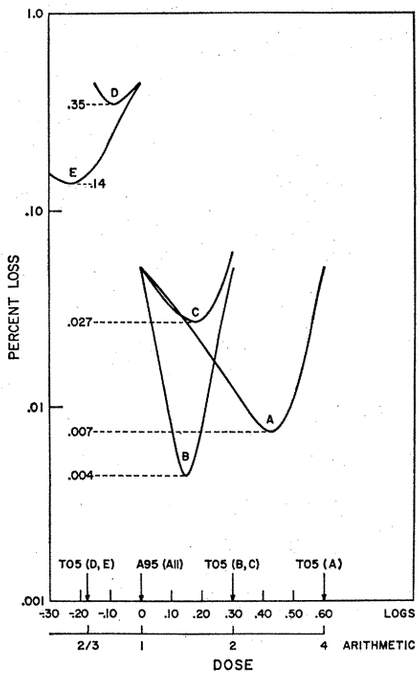

Fig. 1. Loss as related to drug dose ($\lambda = 1$). Minimum loss is shown for each of five hypothetical drugs. The dose at which the minimum loss occurs is the "best" dose.

TO5 + 1.645 σ_T and x = dose (usually $\log_{10}$ of dose) of drug administered. The loss function is then

$$L = \int_{x}^{\infty} \frac{1}{\sqrt{2\pi}\,\sigma_A} \exp\left[-\frac{(t-\mu_A)^2}{2\,\sigma_A^2}\right] dt + \lambda \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi}\,\sigma_T} \exp\left[-\frac{(t-\mu_T)^2}{2\,\sigma_T^2}\right] dt \quad (2)$$

To minimize this function we take the first derivative, and set the result equal to zero and solve for x, the log dose.

The derivative gives

$$L' = -\frac{1}{\sqrt{2\pi}\,\sigma_A} \exp\left[-\frac{(x-\mu_A)^2}{2\,\sigma_A^2}\right] + \frac{\lambda}{\sqrt{2\pi}\,\sigma_T} \exp\left[-\frac{(x-\mu_T)^2}{2\,\sigma_T^2}\right] \quad (3)$$

The general solution (*6*) when the variances are unequal and $\lambda \neq 1$ is

$$x = \frac{(\sigma_T^2\,\mu_A - \sigma_A^2\,\mu_T)}{\sigma_T^2 - \sigma_A^2} + \frac{\sigma_A\,\sigma_T\left[(\mu_A-\mu_T)^2 + 2\,(\sigma_A^2-\sigma_T^2)\ln\lambda\,\frac{\sigma_A}{\sigma_T}\right]^{1/2}}{\sigma_T^2 - \sigma_A^2} \quad (4)$$

In the special case where the slopes of the two dose-response curves are the same $\sigma_A = \sigma_T = \sigma$, we obtain from Eq. 3 (after some algebraic manipulation) the solution for the dose which gives the smallest loss,

$$x = \frac{\mu_A + \mu_T}{2} - \frac{\sigma^2 \ln\lambda}{\mu_T - \mu_A} \quad (5)$$

Under some circumstances $\lambda = 1$ (*7*). This solution then reduces to

$$x = \frac{\mu_A + \mu_T}{2} \quad (6)$$

The loss, by administering the dose x, is found by substituting this value for x in Eq. 2. This gives the minimum loss, and it is in this sense, that x is the "best" dose (*8*).

Table 1 gives the rankings of five hypothetical drugs, first by the therapeutic index, and then by the minimum loss approach, if λ is assumed to be 1. Computations have also been made for a hundred-fold range of λ from 0.1 to 10. The order of ranking is the same as in Table 1 with two exceptions. At $\lambda = 10$, the orders of drugs A and B are reversed. At $\lambda = 0.1$, the orders of drugs D and E are reversed.

Figure 1 shows loss curves for the five hypothetical drugs. When one has complete information about a drug, the therapeutic index is clearly not the proper measure to use for ranking.

Of consequence in Fig. 1 (where it can be seen more clearly than from Eq. 3) is that there can be a "best" dose which lies outside the range A95 to TO5 (Table 1, drug E). The intuitive consideration that almost any dose between the A95 and TO5 would be a "suitable" dose, is thus contradicted. Here the therapeutic index does not give the range within which the best dose will be found. Figure 2 shows the relative loss at different values of λ. The relative loss is given in terms of $L/1+\lambda$, where L is computed from Eq. 2 and $(1+\lambda)$ is a normalizing constant, introduced so that the maximum loss is 100 percent or 1. The ranking of the drugs can be read from this graph starting at the bottom. The drug with the smallest loss is best. For some levels of λ (λ large meaning not very serious illnesses) drug E (therapeutic index is 2/3) leads to less loss than does drug C (at $\lambda \leq 0.5$), a drug with a therapeutic index three times as high. If the loss from drug C is tolerable under these circumstances, then drug E is usable at the levels of λ described, even though the therapeutic index is less than 1.

The major argument left in favor of the therapeutic index is that it is an intuitively satisfying guide when one lacks full knowledge. It may be worthwhile therefore in some situations to gain more knowledge about response curves, and to abandon the therapeutic index as a ranking metameter as one abandons one's ignorance. Since the minimum-loss approach uses more data (that is, slope information) than does the therapeutic index, one should always get better results (in some "expected value" sense) with minimum loss rather than the therapeutic index. The strong possibility exists that for any one individual, the dose at which toxicity occurs is statistically correlated ($\rho \neq 0$) with the dose at which positive response occurs. In the model given here we have assumed that this correlation does not exist. The selection of a best dose given a correlation needs to be investigated, as does the problem of ranking where one is willing to accept a fixed cost of toxicity.

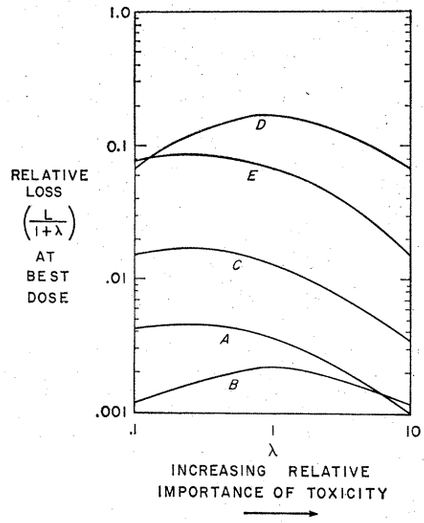

Fig. 2. Relative loss at the best dose as a function of λ. At $\lambda = 1$, the ordinate of each of these curves is one-half that given in Fig. 1 at the minimum loss shown there for each drug.

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5. The concept of "minimum loss," as formulated here, arose from discussions with Jerome Cornfield, now at the National Heart Institute, Bethesda, Md. It is also possible to maximize the "gain" function $G = q_1 - \lambda q_2$, which gives the same best dose as does the minimum loss approach.
6. Equation 4 does not always lead to a real answer. For a real answer the term inside the square root sign must be positive. This is true when $\sigma_A = \sigma_T$, or $\lambda = 1$, or when (i) $\sigma_T > \sigma_A$, then

$$\lambda \leq \frac{\sigma_T}{\sigma_A} \exp\left[-\tfrac{1}{2}\frac{(\mu_A - \mu_T)^2}{\sigma_A^2 - \sigma_T^2}\right],$$

or when (ii) $\sigma_T < \sigma_A$, then

$$\lambda \geq \frac{\sigma_T}{\sigma_A} \exp\left[-\tfrac{1}{2}\frac{(\mu_A - \mu_T)^2}{\sigma_A^2 - \sigma_T^2}\right]$$

It can be shown mathematically that the minimum loss occurs at the solution for x given by the positive value of the square root in Eq. 4. These limitations on λ imply that there are situations in which rankings are not possible (that is, when the conditions are not met). The medical and biological meaning of such a situation must then be thoroughly investigated.
7. The constant, λ, expresses the discomfiture that toxicity causes relative to the discomfiture that failing to cure would create. λ must be substantially larger than 1 when one is more willing to accept the pain and discomfort of an illness, than pain and discomfort induced by a drug. For a mild, self-limiting illness (for example, headache), in which scarcely any drug toxicity is permissible, λ should be large. In a fatal illness, such as acute leukemia, any toxicity less than lethal might be acceptable and λ could possibly be about 1. From Eq. 3 it can be shown that increasing λ will lead to a lowering of the "best" dose. This is reasonable, λ being a measure of the fear of toxicity and since the more we fear toxicity, the more we will try to avoid it. The choice of λ is largely intuitive, and in treating man, the art and sensibilities of the physician must enter. For a specific illness it may be that a range of acceptable λ's can be agreed upon among several physicians.
8. The values of the integrals of Eq. 2 are obtained from using

$$Z_A = \frac{x - \mu_A}{\sigma_A}, \; Z_T = \frac{x - \mu_T}{\sigma_T}$$

as arguments in tables of the normal probability distribution.

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Oxygen Atom Reactions with Condensed Olefins

Abstract. *Gaseous oxygen atoms, thermally generated from O_2 on a 2300°K zirconia surface, react with simple condensed olefins below 100°K. Initial results indicate that the distribution of products differs from that obtained in the gas phase at higher temperatures.*

Oxygen atoms, produced in the gas phase, can react with condensed simple olefins such as propylene and butene. Ponomarev (*1*) has reported a pressure decrease when an iridium filament was made incandescent in a vessel containing oxygen whose walls, maintained at 77°K, were coated with propylene. We have observed a pressure decrease in such a system but found little evidence of reaction. There is formation of carbon dioxide from carbon contamination of the iridium, and excessive evaporation occurs when the filament is heated above 1850°K. The pressure decrease is thus not a reliable indication of reaction.

A particularly suitable device for the thermal production of ground state oxygen atoms is the Nernst glower. This is essentially a zirconia rod that can be electrically heated to a temperature of 2300°K. With an oxygen pressure of 200 millitorr or less, sufficient dissociation occurs that the reaction of oxygen atoms at surfaces may be readily studied. The Nernst glower has the advantage of being inert in the oxygen atmosphere at operating temperatures so that a pressure decrease is a reliable measure of the extent of reaction.

Condensed olefins at 77°K reacted only very slowly with oxygen atoms, while at 90°K the reaction proceeded at a convenient rate. In a typical experiment, propylene condensed and maintained at 90°K, was exposed to oxygen atoms. The pressure was held at 40 millitorr by allowing oxygen to leak slowly into the system. After 10 minutes the glower was switched off, the excess oxygen removed, and the reaction products warmed to room temperature. The product analysis was performed by means of gas chromatography with a 3-meter column of bis [2-(2-methoxyethoxy) ethyl] ether on chromosorb at 50°C. Propionaldehyde, propylene oxide, acetone, acetaldehyde, and some minor products as yet unidentified were found. Owing to its ease of polymerization, formaldehyde is not readily eluted from a chromatographic column. Its presence among the reaction products, however, was indicated by qualitative tests. The propylene oxide : propionaldehyde : acetone ratio was 1.0 : 1.5 : 0.1. Yields of acetaldehyde were about equal to those of propylene oxide. These results are qualitatively similar to those found by Cvetanovic in gas phase studies (*2*).

As the exposure times of the condensed propylene to oxygen atoms were increased, the relative yield of propylene oxide decreased. This is ascribed to a reaction between propylene oxide and oxygen atoms. When propylene oxide alone is diluted with propane, condensed at 90°K, and exposed to oxygen atoms, propionaldehyde, acetone, acetaldehyde, and formaldehyde are produced.

It is significant that reaction between the condensed olefins and oxygen atoms differ from the gas phase results in that neither CO nor CO_2 are formed as reaction products. This indicates that the energy associated with the initial addition of the oxygen atom to the olefin is more efficiently dissipated in condensed phase reactions, and the effects attributable to "hot radical" reactions and rearrangements are at least partially supported.

Butene-1 and oxygen atoms at 90°K yielded α-butene oxide, *n*-butyraldehyde, propionaldehyde, and other minor products. It was observed that for small oxygen atom concentrations, propionaldehyde was the predominant product. High oxygen atom concentrations gave α-butene oxide and *n*-butyraldehyde as major products. In fact, the propionaldehyde yield showed little change with variation in temperature of the zirconia surface. This suggests two separate mechanisms for the three-carbon and four-carbon products. Butene-2 and oxygen atoms yield acetaldehyde and β-butene oxide. Isobutene forms isobutene oxide and acetone. These results differ from those obtained in the gas phase (*3*).

Observation of reactions in the condensed phase at low temperatures affords the advantage of simplicity largely because of the suppression of high activation energy secondary processes. This technique has been demonstrated in studies of the reactions of hydrogen atoms with condensed olefins (*4*). The method can now also be applied to a detailed study of the interaction between oxygen atoms and condensed olefins.

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5. Supported by the USPHS.

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