than the input value of k_e (0.5) or that estimated by Eq. 2. In contrast, the k values estimated by the concentration ratio method correspond well with those estimated by Eq. 2 (0.5). The concentration ratio method performed adequately when the $C_p t$ data were limited (Table II) and even when k_a was larger than k_e by 10% (Table III).

It must be noted that the nonlinear regression analysis of the $C_p t$ data in terms of Eq. 2 represents the most appropriate method to calculate the rate constant for the special case of the one compartment open model where $k_a = k_e$ (Tables I and II). The pharmacokinetic analysis of the data using Eq. 1 with the NONLIN program is, as suggested by Chan and Miller, the only method known to date to identify the equality between k_a and k_e. The proposed concentration ratio method represents a simple, complimental method which can be applied even in those cases with limited, $C_p t$ data when the model is identified *a priori*.

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Problems Involved with Developing a Suitable Model for Evaluating Exposure to Bis(2-ethylhexyl) Phthalate from Medical Devices

In a recent article, "Effect of Renal Failure and Bis(2-ethylhexyl) Phthalate Pretreatment on the Disposition and Metabolism of Antipyrine in the Rat" [1], Pollack and Shen presented an experimental model for studying chronic exposure of hemodialysis patients to bis(2-ethylhexyl) phthalate (I) [also known as di-2-ethylhexyl phthalate or DEHP]. Their model, however, utilized oral administration (intragastric intubation) of I rather than a parenteral route. Since the authors did not demonstrate that the effects of I upon antipyrine metabolism and disposition were the same when I was administered orally as when it is given parenterally, one must question acceptance of this as a suitable model for evaluating I exposures from hemodialyzers or other medical devices.

A number of reports, including those of Albro and Thomas[2], Rowland[3], and Lake *et al.*[4], indicate that orally administered I leads to absorption primarily of its hydrolytic product, mono-2-ethylhexyl phthalate or MEHP (II). Therefore, the proposed model[1] should be suitable for evaluating exposure to I from food packagings or other oral exposure, but in order for it to be accepted as a suitable model for clinical exposure to I from medical devices it will be necessary to demonstrate that the parameters evaluated are not affected by the route of administration of I.

There is no dispute that I is metabolized *in vivo* to produce II along with other metabolic products. However, the unanswered question in this case is whether or not the diester (I), to which the patient would initially be exposed intravenously during hemodialysis, *etc.*, would produce qualitatively and quantitatively similar effects on antipyrine metabolism and disposition prior to its metabolic conversion, as would the monoester (II) and other metabolic products. A number of reports have indicated differences in biological activity between I and II, or oral *versus* parenteral administration of I. Some of these reported differences include acute LD_{50}[5], *mutagenicity in bacterial systems*[6], *pentobarbital sleeping time* and effects on aminopyrine-*N*-demethylase and aniline hydroxylase[7], and mitochondrial (state 3) respiration[8].

The authors[1] commented on the findings of Agarwal *et al.*[7], that effects on enzyme activities were associated with the route of I administration, but then they dismiss these findings by attributing the differences to doses administered, not route of administration. However, an examination of the data[7] reveal that when an enzyme or biochemical system was affected by oral or parenteral administration of I (*a*) there was generally a dose-related response, and (*b*) comparisons of similar doses (5.2 and 13.0 po *versus* 5.0 and 10.0 ip) often produced markedly different responses.

Thus, because of the various literature reports (a few of which were cited) showing or suggesting a difference in biological activity between I and II or II plus other metabolites, the model proposed to study the effects of I, from artificial kidneys or other medical device exposure, on antipyrine metabolism and disposition cannot be accepted until it is demonstrated that I produces the same effects on these parameters when administered parenterally as when given by gastric intubation.

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