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Editorial Views

*On Species Differences. 2. Computers**

It is well known that species differences in drug metabolism invalidate indiscriminate transfer to man of quantitative data obtained from animal studies (Brodie: Clin. Pharmacol. Ther. 3: 374, 1962). To this dictum should be appended the concept that digital computers, analog computers and biological models are also to be classified as animal species. An important difference from other species is that, while findings obtained in studies with experimental animals are conditioned by the characteristics of the species concerned, the results of computer analysis reflect the validity and all-inclusiveness of the input data. Indeed, computers are unique and valuable animals. Existing only to serve man, they require a complete diet of facts, preferably raw, occasionally predigested, but under no circumstances containing artificial flavor, color and other additives. Deprived of vitamins, essential minerals, even important trace elements, they disgorge indigestible (but neatly packaged) masses of misinformation.

The consequences of failure to recognize these precepts may be inherent, in this issue, in an article titled "The Effect of Thiopental Metabolism on Duration of Anesthesia," by Drs. L. J. Saidman and E. I. Eger, II. While the authors deserve credit for willingness to re-examine a discarded concept, their work must be examined for possible flaws in execution.

The report itself consists of two unrelated components. The first deals with hepatic extraction of thiopental in the dog, a species in which thiopental is transformed far more slowly (5 per cent per hour) than in man (Brodie and others: J. Pharmacol. 109: 26, 1953). Because of this species difference, metabolic data from studies with dogs are inapplicable to events in man, hence to be debated in this paper.

The second part, concerning analog computer analysis of thiopental distribution and metabolism, contains no original data but is based wholly upon the findings of others. The main thesis of the paper, depicted graphically in figure 6, is that metabolism is of major importance in the early rapid reduction of arterial thiopental levels following injection and in the early awakening seen with this anesthetic in man. The presentation may be flawed by two inadequately verified but crucial assumptions and perhaps one vital omission.

The first assumption is validity of transfer to normal man of our hepatic venous catheterization data, obtained primarily from abnormal patients with liver disease (Mark and others: Nature 206: 1117, 1965). Six of our subjects showed transhepatic arteriovenous differences (*i.e.*, extraction of thiopental by liver) ranging from 10 to 50 per cent, with a mean value of 28 per cent. Extraction in the remaining 5 cirrhotic subjects was within the analytical error of the method; these patients obviously had severe hepatic impairment. Our report did

* For previous editorial comment see ANESTHESIOLOGY 19: 799, 1958.

include one subject with a normal liver in whom the transhepatic difference in thiopental concentration was 32 to 35 per cent. Consequently the 30 per cent figure for hepatic extraction chosen by the authors for normal man is probably not unreasonable; whether it is the most appropriate value remains to be determined. (Our own continuing studies in normal man are too preliminary for use.) The problem is further complicated by individual variability within the heterogeneous human species (Brodie: *loc. cit.*, 1962).

A second important assumption, that the hepatic percentage extraction is constant at both early and late times and regardless of the concentration of thiopental in arterial blood, is based on data obtained from animal liver preparations *in vitro* (Gould and Shideman: J. Pharmacol. 104: 427, 1952). Direct evidence for this phenomenon in human liver *in vivo* has yet to be obtained. In an unrelated chemical family, differences *in vivo* were shown with sulfobromophthalein in the dog. Diminution of the rate constant for removal by liver occurred with increasing dosage, indicating saturation (Goresky: Amer. J. Physiol. 207: 13, 1964).

A third possible discrepancy arises in connection with the body fat compartment. The authors, by indiscriminately borrowing all the parameter data from a previous computer solution (Price and others: Clin. Pharmacol. Ther. 1: 16, 1960), perpetuate the errors of that solution in underestimating rate and extent of uptake of thiopental by adipose tissue. They state that the amount of thiopental in fat is 17 per cent at 20 minutes, 21 per cent at 51 minutes and, from figure 6, 25 per cent at 100 minutes, by which time metabolism has accounted for 38 per cent of the dose. Our own published data obtained from fat biopsies in human subjects (Mark and Brand: Bull. N. Y. Acad. Med. 40: 476, 1964) show that by 90 minutes following administration 50 per cent of the thiopental injected has found its way into adipose tissue, comparable to human findings by others (Shideman and others: J. Pharmacol. 107: 368, 1953) and 100 per cent higher than the present computer estimate. This is also contrary to the authors' assertion that uptake by fat never exceeds the contribution of metabolism. In addition, a preliminary report (Brand and others: Fed. Proc. 22: 479, 1963) revealed maximum fat/plasma thiopental concentration ratios of 14 to 18 at 5 hours, considerably higher than the partition coefficient of 11 presented to the computer.

A basic tenet in dealing with species differences is that hypotheses of drug action derived from studies in animals must be verified (or disproved) in man. Similarly, if a theoretical computer solution is in disagreement with actual findings in man, the computer solution must yield. While the previous computer study antedated publication of the above corrective data concerning thiopental uptake by human adipose tissue, omission of these data from the present study is regrettable. Obviously, with the establishment of a role for fat uptake double that predicted by the present computer solution, the contribution of metabolism during the period of major uptake by fat (*i.e.*, from 30 to 90 minutes following injection) must be correspondingly lessened.

It is probably quite correct to state that early awakening (within the first 20 to 30 minutes) following a single injection of thiopental is due primarily to redistribution of drug from viscera and blood to lean mass and fat, with a modest but as yet imprecisely defined contribution by metabolism. It may not be correct to state that metabolism plays a major role in early awakening. Duration of sleep in our two small groups of subjects with cirrhosis was identical (2 to 19 minutes in the severely impaired group, 4 to 15 minutes in the other) despite our inability to demonstrate significant metabolism in the first group.

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