

discard material which showed evidence of breakdown with increasing time. Figure 2 shows the effect of the (presumed) presence of moisture on the silylation reaction. Purging of the vial with nitrogen prior to silylation resulted in the reaction reaching completion by about 90 minutes and the derivative remaining stable for many hours. No deterioration was observed for those samples held for up to 24 hours. When moisture was present the same amount of product was formed, but at a slower rate, and breakdown of the derivative followed fairly rapidly.

The two main metabolites of Ibuprofen were not silylated under the conditions outlined. The derivatisation of these compounds required, in addition to BSA, the presence of the compound trimethylchlorosilane (Phase Separation Ltd.).

The drop in urinary drug values showed a biphasic pattern, as had been observed in the earlier experiment, with an 89% drop in values over the first 170 minutes, followed by a steady decrease over the next 20 hours. The drug had nearly disappeared by about 28 hours. The amount of unchanged drug excreted, as a percentage of

dose given, was very much smaller in the experiment using pulverised tablets, being only about 2% (Figure 4). The two figures given may not represent percentages of drug absorbed since there is no information concerning excretion by routes other than urine.

The rate of absorption is faster than that reported in the literature for man, rabbit and dog where figures of 90 minutes were reported (Adams, Bough et al, 1969; Mills, Adams et al, 1973) but slower than the 20 minutes reported for the rat (Adams, Bough et al, 1969).

The small percentage of unchanged drug appearing in the urine is in agreement with studies on other species (Mills, Adams et al, 1973).

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DISCUSSION

TOBIN: I was very surprised at the difference between the urinary levels for the tablets and the pure drug. Have you any hypothesis or explanation?

LAMBERT: Not unless it is the fact that it was two completely different preparations, the bioavailability could be different. The drug was a crystalline powder supplied by the manufacturer. The tablets we pulverised because it is not easy to give 30 tablets and we thought it better to wash it down.

HUNT: Can you indicate the status of the metabolites please?

LAMBERT: (using overhead projector) Adams a co-worker did most of this work. These come out quite well once you add the other catalyst. Metabolite A is the 2-4-2 hydroxy 2 methyl propyl phenyl propionic acid, the other on is Metabolite B: 2-4-2 carboxy propyl phenyl propionic acid. We found we were getting something like 6% of the Ibuprofen and then about 60% of metabolite A, and then metabolite B following that. We have no experience of the other two metabolites which have only been found in one animal, I think the dog. These are the two commonest metabolites. You have your hydroxy group and your initial acidic group, obviously they seem to be more difficult to silylate.

HUNT: Can you comment on the stereoisomerism?

LAMBERT: Not of these. He has done some work on Ibuprofen, the plus and minus enantiomers. Most of the work has been done by Boots, they developed the earlier methods of gas chromatography. We were working at the same time but with an interest in a method for greyhounds.

JACKSON: Did you study the excipient in the tablet?

LAMBERT: No, this could be the factor involved in the difference in absorption. It was 30 minutes. The pure drug was 63 minutes and the tablets 30 minutes. So in fact it was going in faster in tablet form, it does not stay long. I don't know the pharmacological effect on the horse or what effect this might have. What I have observed is that the horse seemed to get quieter, but this was only one horse.
