A COMPARISON OF DIAMORPHINE-WITH-COCAINE AND METHADONE

Dr Twycross (1977) compared diamorphine-with-cocaine and methadone and hints that he has identified a potential problem but does not solve it. From his first paragraph it would appear his reason for the comparison was to examine Lipman's (1975) contention that the duration of analgesia from methadone is considerably longer than that from diamorphine. If this were true, his trial design of treating both groups of patients at identical dosage intervals would be inappropriate since drug would be bound to accumulate in one group with possible toxic consequences and the patients in that group would also suffer unnecessary disturbance. We prefer to believe that from his own wide experience he expected similar durations of analgesia at least in his patients at St Christopher's Hospice. That would also be our expectation as compilers of the methadone data sheet to which he refers. Admittedly, the literature which both he and we use requires some assumptions about like behaviour of related drugs because of limited freedom to study narcotics. Allowances must be made for work in these very difficult studies and in particular for the necessity of prescribing many extra drugs in an uncontrolled manner but we are still puzzled by his conclusion that methadone treatment positively hastened the death of patients and thus caused the trial to be stopped after only one month for ethical reasons. The monthly death rates reported during autumn 1975 among patients who did not receive methadone were so variable that another explanation is possible. Therefore the contention that in its most common mode of usage methadone accumulates to create a special danger is illustrated only by a single and brief report (Symonds, 1977) of a patient who might well have had deficiencies in excretory, metabolic or plasma protein binding capacity to explain her unexpected sensitivity to methadone on repeated dosage.

The analgesic effect of methadone is not closely related to plasma concentration but other effects are. Moreover after the analgesic effect of a single dose has waned the other effects persist. Regular dosing of methadone to secure continuous analgesia will therefore cause accumulation as Dr Twycross says. But accumulation is not indefinite, for eventually the elimination rate should match the administration rate, and it is not *necessarily* dangerous. Dangers thought to result from the inevitable accumulation need reasonably positive identification before inclusion in the data sheet because if indeed 'methadone is a satisfactory substitute for diamorphine in some patients' the evaluation of the danger-benefit ratio is not a trivial matter.

In discussing the dangers of methadone accumulation, mention should surely be made of tolerance and enzyme induction. Tolerance of its effects is taken for granted in prescribing methadone for heroin addiction where doses are as large as those used in treating terminal cancer (Verebely, Volavka, Mule & Resnick, 1975); and chronic oral dosing with methadone has been shown to increase its metabolism in at least two mammalian species (Masten, Peterson, Burkhalter & Way, 1974; Misra, Mule, Bloch & Vadlamani, 1973).

Discussion of the rudiments of therapeutics and the art of the wise use of any narcotic is inappropriate in a data sheet. But given the limitations in the present knowledge, in what way could the data sheet be amended that would benefit patients?

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