Journal of Chromatography, 223 (1981) 484—485
Biomedical Applications
Elsevier Scientific Publishing Company, Amsterdam — Printed in The Netherlands

CHROMBIO. 811

Letter to the Editor

Comments to the article "Improved gas chromatographic method of determining diclofenac in plasma"

Sir,

We have been engaged in the measurement of diclofenac in human plasma, using the method of Geiger et al. [1], for over four years and were naturally interested in a recent claim by Ikeda et al. [2] of an improvement in the method. However, after a very careful study of the paper, we feel that the following comments are necessary:

(1) The "improvement" reported is based on a claim that a three-fold increase in sensitivity can be obtained by the addition of methanol to the derivatization medium, trifluoroethanol (TFE) containing 0.5% sulphuric acid. On the basis that this mixture resulted predominantly in the methyl ester rather than the indolone, they then completely replaced trifluoroethanol with methanol or ethanol in 0.1 or 0.5% sulphuric acid. Since Geiger et al. demonstrated almost 100% conversion to the indolone, we find the claim of Ikeda et al. difficult to understand. It is hard to imagine that the detector response to the ester should be three times that of the indolone.

We compared derivatization with TFE, TFE + methanol and methanol alone, each containing 0.5% sulphuric acid. The results are presented in Table I. An internal standard, CGP 4287, was used and this mimics closely the partition

TABLE I

MEAN PEAK HEIGHT RATIO (DICLOFENAC/CGP 4287) AND ABSOLUTE PEAK HEIGHT OF DICLOFENAC AFTER THE DERIVATIZATION PROCEDURES DISCUSSED IN THE TEXT

$n = 10$.

Derivatization procedure	Peak height ratio (mean ± S.D.)	Peak height of diclofenac (mm)
Trifluoroethanol	1.089 ± 0.14	70
Trifluoroethanol + methanol	0.954 ± 0.08	69
Trifluoroethanol	0.811 ± 0.07	90
Methanol	0.951 ± 0.12	92

0378-4347/81/0000—0000/$02.50

characteristics of diclofenac and is derivatized in the same way. For this reason we have presented our results as peak height ratios but we have also included the absolute peak height of diclofenac. Ikeda et al. use aldrin as a gas chromatography standard added immediately before injection. It can be seen that neither of the proposed modifications resulted in increased sensitivity.

(2) Ikeda et al. do not report measurements below 100 ng/ml while Geiger et al. claim that their method is capable of measuring diclofenac down to 2 ng/ml. After a 25-mg oral dose in man, measurement below 100 ng/ml is required for pharmacokinetic studies.

(3) The only modification we have found necessary during our four years' experience with the method of Geiger et al. is the substitution of *n*-heptane for benzene because of the carcinogenic hazard associated with the latter. We are surprised that Ikeda et al. did not consider this worthwhile.

In conclusion, we feel strongly that papers with the word "improved" in their titles should be scrutinized very carefully, before publication, in order to ensure that there is, indeed, a significant improvement before being allowed to become part of the established literature.

NOTE ADDED IN PROOF

After having considered additional information from Ikeda et al. and after further investigations of our own we should like to add the following to our comments:

(A) Derivatization of diclofenac with methanol in 0.1% sulphuric acid results in the methyl ester which, with our equipment, produces an increased response (66%) from the electron-capture detector.

(B) The use of "old", rather than fresh, potassium hydrogen carbonate, results in conversion of the ester to the indolone with a consequent reduction in peak height (under our conditions the retention times of methyl ester and indolone are identical). "Old" bicarbonate is considerably more alkaline than "fresh" due to the formation of carbonate on standing. We understand that Ikeda et al. now favour washing the methyl ester with water.

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2 M. Ikeda, M. Kawase, M. Hiramatsu, K. Hirota and S. Ohmori, J. Chromatogr., 183 (1980) 41.

(Received August 28th, 1980)