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179. Eino Nelson : Physicochemical Factors Influencing the Absorption of Erythromycin and its Esters.

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It has been reported that within a series of esters of erythromycin prepared with low molecular weight aliphatic acids, the propionyl ester gave considerably higher blood levels after oral administration than others in the series as well as higher levels than erythromycin itself.[1] On the basis of findings from past work dealing with dissolution rates of drugs,[2~4] it seemed reasonable to believe that their absorption under eqivalent conditions of administration was related to their dissolution rate in both gastric fluid and intestinal fluids, particularly since erythromycin and its esters are rapidly destroyed in solution in acidic mediums.[5] The work to be described now consisted of making dissolution rate determinations on erythromycin and some of its esters in fluids simulating gastric and intestinal fluids with respect to hydrogen ion concentration and on examining the relationship between these rates and the results of the clinical work.[1]

Experimental

Dissolution rate determinations were made using thin, cylindrical discs prepared by compressing powdered erythromycin or some of its esters*2 (Table I) using standard tableting machine punches and dies in a Carver press modified for this purpose. The discs were about 1.27 cm. in diameter, about 0.3 cm. thick and were pressed at a pressure of about 2000 kg./cm^2. The discs were mounted into the end of special brass holder (see Fig. 1) with molten paraffin and most of the holder itself also coated with the same material. The exposed faces of the discs were not coated. The disc holders with mounted discs were allowed to come to weight equilibrium at room temperature and then mounted into a chuck on the shaft of synchronous motor that had a rotational speed of 500 r.p.m. In a given test, the disc holder with disc assembled as previously described was lowered to a depth of about 2 cm. into the test medium and stirring immediately commenced.*3 Stirring continued for appropriate times as determined from preliminary experiments as being necessary to cause the dissolution of weighable amounts of drug. Medium temperature was between 23~26°. The disc with holder was removed at the end of an experiment, briefly rinsed with distilled H_2O and then alowed to reach weight equilibrium at room temperature. By weighing, the amount of material lost by dissolution could be determined and this was expressed as mg./cm^2/min.

The test mediums used were 0.1*N* HCl to simulate gastric fluid with respect to pH and 0.1*M* H_3BO_3 adjusted to pH 7.4 with NaOH to simulate intestinal fluid with respect to pH. Volumes of solution chosen for dissolution experiments were 500 or 1000 ml. in order to insure that dissolution took place into a medium that was infinite in extent for all practical purposes. In some cases, pieces of drug were lost from the faces of the discs and data collected in these tests were not used. Five to ten independent determinations were made on each of the drugs studied. The discs presented a constant surface area to dissolution medium, hence an absolute comparison of rates was obtained under the conditions of the test.

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1) V.C. Stephens, and J.W. Conine : Antibiotics Annual, 1958~1959, p. 346 (1959), Medical Encyclopedia, Inc., New York, N. Y.

2) E. Nelson : J. Am. Pharm. Assoc., Sci. Ed., **46**, 607 (1957).

3) *Idem* : *Ibid.*, **48**, 96 (1959).

4) E. Nelson, and I. Schaldemose : *Ibid.*, **48**, 489(1959).

5) H. W. Murphy : Antibiotics Annul, 1953~1954, p. 500 (1953), Medical Encyclopedia, Inc New York, N. Y.

Results and Discussion

The dissolution rates found are listed in Table I. In order to relate these rates to results obtained with the same esters in clinical trials, blood level data from the latter trials[1] were graphed for those substances that gave measurable levels and the area beneath the curve determined by graphical integration. The area beneath a blood level curve is a measure of the amount of a given drug absorbed.[6] When these areas were compared to dissolution rate in 0.1*N* hydrochloric acid, it was found that an inverse relationship existed between these quantities as shown in Fig. 2. This meant that in the range of dissolution rates in 0.1*N* hydrochloric acid found in these studies, the more slowly dissolving the ester, the greater the amount of drug eventually absorbed. When the areas beneath the blood level curves were compared to dissolution rates at pH 7.4, a direct relationship existed between these quantities as shown in Fig. 3. This relationship did not hold for erythromycin or its acetate. These results allow the following interpretation of the clinical work. With erythromycin propionate (which had the largest area beneath its blood level curve), a balance was struck between absorbability after leaving the stomach as reflected in its having the most rapid dissolution rate in neutral medium and conservation of the dose as reflected in its possessing the slowest dissolution rate of the series in acidic medium. The fact that the relationship implied by Fig. 3 did not hold for erythromycin and its acetate may be explained as follows : With esters possessing dissolution rates in neutral medium, at least that of the order observed for erythromycin propionate, the limiting factor in absorption is conservation of the dose by slow dissolution in acidic medium. The clinical work[1] included studies with esters other than those discussed now. However, none of these others gave measurable blood levels. Preliminary experiments here indicated that dissolution rate of these materials was much slower in both acidic and neutral medium than any of the other esters studied.

Table I. Dissolution Rate of Erythromycin and its Esters in Simulated Gastric and Intestinal Fluids[a]

No.	Compound	Rate in 0.1*N* HCl[b]	Rate in 0.1*N* Borate (pH=7.4)[c]
6	Erythromycin	4.24 (2.10)	328 (29.3)
2	Erythromycin acetate	1.61 (0.37)	120 (28.5)
3	Erythromycin acrylate	2.06 (0.97)	8.91 (0.300)
1	Erythromycin propionate	1.24 (0.24)	16.5 (0.526)
5	Erythromycin butyrate	2.92 (0.32)	1.44 (1.18)
4	Erythromycin isobutyrate	2.74 (0.58)	3.63 (1.28)

a) Rate shown with standard deviation in brackets
b) mg./min./cm^2
c) mg./min./cm^2 × 10^3

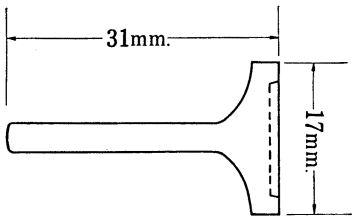

Fig. 1. Illustrating the Disc Holder used in Dissolution Rate Studies

6) J.G. Wagner, O.S. Carpenter, E.J. Collins : J. Pharmacol. and Exptl. Therap., **129**, 101(1960).

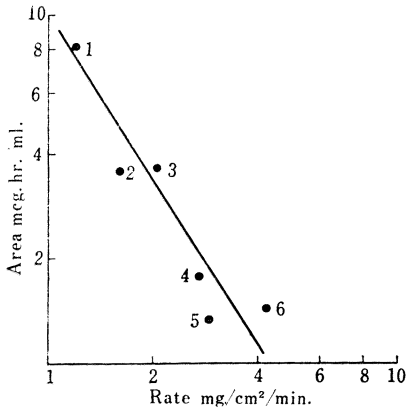

Fig. 2. Showing the Relationship between Area beneath Erythromycin Blood Level Curves and the Dissolution Rate of Various Forms in 0.1*N* HCl. Numbers refer to number of compound as listed in Table I.

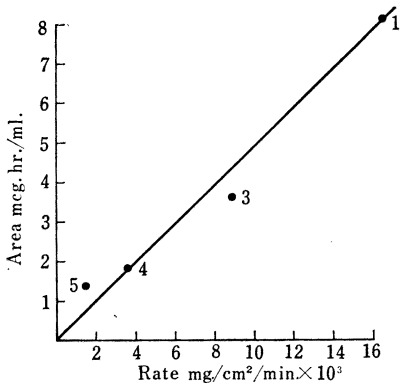

Fig. 3. Showing the Relationship between Area beneath Erythromycin Blood Level Curves and the Dissolution Rate of Various Forms of this Drug in 0.1*M* Borate Buffer pH 7.4. Numbers refer to number of compound as listed in Table I.

Factors other than solution kinetics are, of course, involved in drug absorption. However, the slow rate of dissolution of all substances in neutral medium strongly suggests that the rate-limiting step in absorption is dissolution of drug in fluids at the absorption sited.

While it is not known that the particle size distribution of erythromycin and its esters, administered in capsules in the clinical trials, was the same, it should be safe to assume that the drugs would have been processed in a generally similar manner prior to encapsulating and therefore contained particles of roughly the same size.

It has been observed that between extremes of large and fine particles, erythromycin blood levels from administration of the propionate do not correlate closely with particle size.[7] Also, that blood levels after administration of either very fine or very large particles are low.[7] These observations support the explanation offered for differences found amongst the several other esters.

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7) Personal communication from Drs. V.C. Stephens and H.W. Murphy, Eli Lilly and Co., Indianapolis, Indiana.