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This Week's Citation Classic

Paterson J W, Conolly M E, Dollery C T, Hayes A & Cooper R G.
The pharmacodynamics and metabolism of propranolol in man.
Pharmacologia Clinica 2:127-33, 1970.
[Dept. Clin. Pharmacol., Royal Postgrad. Med. Sch., London, and Dept. Biochem., Imperial Chem. Industries, Macclesfield, Cheshire, England]

This paper was the first full study of the pharmacokinetics of propranolol after both intravenous and oral administration in man. It also described a method for quantifying the pharmacological response to propranolol using intravenous isoprenaline. The method was used to correlate pharmacodynamics with pharmacokinetics following administration of propranolol in man. [The *SCI*® indicates that this paper has been cited over 245 times since 1970.]

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"At the time this project was conceived, I was working as a Wellcome Fellow in clinical pharmacology with Colin Dollery at the Royal Postgraduate Medical School. We were concerned with the pharmacology of beta adrenoceptor antagonists in man as there was then considerable controversy about the mechanism of action of propranolol in the treatment of angina, hypertension, and arrhythmias. The problem was handicapped by the lack of adequate kinetic data in man and the lack of a suitable method of quantifying beta blockade in human subjects. At that time, beta blockade was measured in man by using a dose of isoprenaline sufficient to cause a pulse rate rise of up to 40 beats per minute and then finding the dose of propranolol to prevent this tachycardia. This dose was then defined as the 'beta blocking dose.' The doses of propranolol used in therapy were larger than these, and so other properties of the drug were proposed to explain the therapeutic effect. As propranolol had been shown to be a competitive beta blocker in the laboratory, it appeared to us that the concept of a 'beta blocking dose' was erroneous. It also seemed unreasonable to comment on the variation in dose required to give a therapeutic effect without adequate kinetic data. Fortunately, Alan Hayes of Imperial Chemical Industries was concerned about obtaining accurate kinetic data in man. Previous studies with conventional assay techniques using nonradioactive material were difficult to interpret as the blood levels seen in man at therapeutic doses were near the lower limits of assay sensitivity. We thus set up a joint study to explore the concept of the 'beta blocking dose' and the kinetics of propranolol using ^{14}C labelled drugs. This was an exciting project in which the expertise and resources of the academic department at the Royal Postgraduate Medical School and the industrial laboratory at Imperial Chemical Industries produced very fruitful results. I well remember carrying out the initial studies on myself as subject, and Figures 2 and 3 in the paper show that data. These studies showed that in man, propranolol exhibited the characteristics of competitive receptor blockade and that the concept of complete beta-receptor blockade was not tenable.

"The kinetic data demonstrated that after oral administration the drug was completely absorbed, and that peak blood levels of propranolol and 4-hydroxy propranolol (a metabolite with beta blocking properties) were seen 1¼ hours after administration. The isoprenaline dose-response studies confirmed that the maximum degree of beta blockade occurred at the same time. No 4-hydroxy propranolol was seen after intravenous administration and so we correlated plasma levels of propranolol given intravenously with the degree of beta blockade measured with isoprenaline. This was the first demonstration that the degree of beta blockade was related to the plasma level of propranolol.

"I believe that the paper is frequently cited for two main reasons. First, it completely changed clinical thinking on the meaning of beta blockade in man and on the techniques which should be used in its assessment. For a recent review of this problem see McDevitt.[1] Secondly, it was the first adequate kinetic study in man and demonstrated the formation of an active metabolite after oral but not intravenous administration. For a recent review of the kinetics of propranolol see Routledge and Shand."[2]

1. McDevitt D G. The assessment of beta-adrenoceptor blocking drugs in man. *Brit. J. Clin. Pharmacol.* 4:413-25, 1977.
2. Routledge P A & Shand D G. Clinical pharmacokinetics of propranolol. *Clin. Pharmacokinet.* 4:73-90, 1979.