# Comparison of some properties of pronethalol and propranolol

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## *Commentary by*

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We published a summary of the properties of pronethalol in 1962, although it was referred to then as nethalide, 'Alderlin'. Alderlin, derived from Alderly Park, ICI's Research Headquarters, was to be the trademark of the new drug. Alderlin didn't make the grade. Propranolol did and was marketed as Inderal, an anagram of Alderlin. Later on, practolol, the first $\beta_1$-selective antagonist was marketed as Eraldin – another anagram! So Alderlin lived on.

The 1962 paper had the title "Pharmacology of an adrenergic beta-receptor-blocking compound". For a paper published in The Lancet, this was brash. The language of receptors and receptor antagonists was, at that time, an argot restricted to pharmacologists with theoretical interests. Clinicians and endocrinologists did not talk about receptors and their antagonists. Now look what's happened!

Although the thalidomide tragedy was developing at the same time as we were developing pronethalol and propranolol, the scientific and legal fallout didn't start until the beginning of 1964 when the Committee on Safety of Drugs opened for business. So the preclinical laboratory studies on these drugs were never officially scrutinised. The growth of local hospital Ethics Committees also came much later on. However, looking back I think the volunteers and patients involved in the early studies were well looked after. Edward Paget, ICI's Head of Toxicology at that time, was way ahead of his time. He was the first to insist on seven days a week dosing and on the instigation of two year carcinogenic tests as soon as the drug was in the earliest stages of clinical development. Hence the discovery of thymic lymphosarcomas in mice associated with prolonged exposure to pronethalol leading to its rapid withdrawal from the clinical scene. In lieu of official regulatory agencies, we had Professor Tony Dornhorst. He was to supervise the first human studies. At our invitation he spent two days in our labs reviewing all our data. I showed him how with high doses, pronethalolol produced cutaneous vasodilatation in dogs associated with tremors and stiffness of the legs. "These dogs look cold to me" he said, "Have you measured their temperature?" I hadn't. So it was my turn to develop a marked cutaneous vasodilatation!

The paper itself is an *in vitro* and *in vivo* comparison of the efficacy of pronethalol and propranololol. I am surprised now how much effort we put in to correlating biological and metabolic half-lives. I doubt if as much effort would be put in today in spite of the critical regulatory environment. The measurement of $LD_{50}$'s would also never be done today. However, the whole point of the $LD_{50}$ test was that you could get an estimate of the error variance. The test fell into disrepute because of the large number of animals needed and the large confidence limits. So nowadays we do toxicity tests where we cannot measure an error variance and so can feel much more comfortable about things!

The big surprise for me is that we never mention in this paper Brian Prichard and his discovery of the hypotensive action of both pronethalol and propranolol. By the time we wrote the paper he had shown that pronethalol produced small reductions in diastolic pressures of normotensive subjects taking part in an antianginal trial. He had also reported a small study showing that propranolol produced much larger reductions in hypertensive subjects. Prichard took years to convince sceptical cardiologists about the reality and importance of his observations. Were we sceptical too?

This was a valedictory paper. By the time it was published, Duncan and I had left ICI to go histamine hunting.

## References

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