Current Trends in Benzodiazepine Research

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Thank you for inviting me as a guest speaker to this 30th anniversary of the Pharmaceutical Society of Korea. I take it as a compliment to my firm F. Hoffmann-La Roche and Co., which, has not only discovered and introduced the benzodiazepines, but has since then been continually in the fore-front of this research. As my subject is going to be “Current Trends in Benzodiazepine Research” I will try to have a look into pending problems. The history of the benzodiazepines has been told several times (e.g. Sternbach, Haefely).

The benzodiazepines are by themselves a highly interesting group of drugs. In the last few years many new doors have been opened by research with a view on new territories to be explored. Besides the scientific interest of progress in benzodiazepine research, some problems this research meets can be taken as an example for many other areas of pharmaceutical research. Thus a few thoughts on pharmaceutical and medical treatment in general will be pot forward; the benzodiazepines can serve as an example for these more general problems.

Before discussing some main trends in benzodiazepine research let us have a very short look back into the history of scientific thought of which medicine has become a branch, however late this happened.

This exposé will be structured in the following way:

Scientific Thought in Medicine, Chemistry, Basic Pharmacology, Pharmacokinetics, Clinical Research, Postmarketing Surveillance, Social Aspects, Conclusion.

SCIENTIFIC THOUGHT IN MEDICINE

Science in the modern sense has been born in the last five hundred years. It is characterised by the willingness to be taught by reality. The basis of our concepts stems from observation. From there hypotheses are created. These are accepted or discarded according to the results of special questioning of nature by further observation or by experiments.

In medicine the first step, accepting observation as the basis of our concepts, can be roughly dated back to the French Revolution (or around 1800). Experimental thinking was introduced in medicine by Claude Bernard roughly a hundred years ago. Systematic application of statistical thinking started about fifty and measuring therapeutic results in controlled clinical trials about thirty years ago.

Two points are essential. Scientific thought, based on observation, excludes a priori dogmatism on one side and reliance on anecdotal evidence on the other side.

CHEMISTRY

Probably more than five thousand chemical entities of the benzodiazepine class have been
synthetized and screened for biological actions. If they are active at all most of them are characterised by a varying association of anxiolytic, anticonvulsive, sedative and muscle-relaxant action. Why then go on with this sort of chemical research? Three reasons can be given.

There is still hope that molecules might be found which are much more selective in their action than those found up to now. It might be therapeutically interesting to have for instance an anxiolytic or an anticonvulsive drug without sedative effect.

The discovery of a selective antagonist of benzodiazepine action among newly synthetized imidazobenzodiazepine (Ro 15~1788) was recently published by Hunkeler et al. of our firm. Its main action is described in the section on pharmacology.

Another hope is that by further molecular variation new biological activities might be found. One such action was detected in our laboratories in a few benzodiazepines which was surprising enough, namely a schistosomicidal action. There is, however, still a strong sedative effect combined with this action. Perhaps there will be ways to overcome this disadvantage by simultaneous application of a benzodiazepine antagonist.

**BASIC PHARMACOLOGY**

New lines have been opened. The mechanism of action of the benzodiazepines has been elucidated to a large extent. Benzodiazepines act by enhancing the effect of GABA-ergic systems, that is, by enhancing pre-and postsynaptic inhibition in the central nervous system. Pursuing this research systematically specific benzodiazepine receptors have been established, first by saturation experiments and then by electron microscopy. They are situated in close neighbourhood to GABA-ergic receptors, but different from them. This leads to understanding the action of benzodiazepines right down to the molecular level and opens new ways for understanding their pharmacokinetics.

Of late, highly specific antagonists of benzodiazepines have been found. They prevent or reverse the effects of active benzodiazepines in conflict tests, their anticonvulsant effects (without being convulsive or pro-convulsive themselves), their sedative and muscle-relaxant action, their effects on the cat spinal cord and on the EEG of rats. In some aspects the situation can be compared with the narcotic antagonists. However, so far no indication has been found for internal ligands as they exist for morphine.

A large field for research in the laboratory and in patients has been opened by these new discoveries. But even understanding the mode of action right down to the molecular level will still leave one problem, the relation between the somatic changes and the psychological factors. The primary factor in an anxiety reaction of an average patient is probably not a spontaneous change on the molecular level, but a psychical, biographical influence. Clinical research of the last decade has brought forward more and more evidence for the importance of psychological and biographical factors, not only for the so called psychosomatic conditions, but even for cancer growth.

**PHARMACOKINETICS**

Sophisticated analytical methods have allowed to follow blood concentrations of benzodiazepines even when they are given in low doses. This