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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 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

has made possible for instance bioavailability studies which are of great value. However, blood levels of benzodiazepines is not the decisive factor for their therapeutic action. One (or two) further compartments need to be considered, the tissue after the blood-brain-barrier and then and foremost the receptor site, when therapeutic action should be correlated with drug concentration. In recent years beta-halflife-times of the blood have been taken by some as an indicator of the length of pharmacological action. This is defeated, not only by purelly pharmacokinetic arguments (not the blood concentration, but what goes on at the receptor site decides on action), but also on clinical grounds (many authors have stressed the in consistency between beta-halflives and duration of action). In the all too easy equation of beta half-life time and duration of action dogmatic thought has crept in again; it shows that scientific thinking has not yet conquered all aspects of medicine. What is needed from a clinical point of view is a kinetic of the therapeutic effects. This has been postulated in recent years; there remains a vast field for research. The situation has been summarized by a slogan "all in life is not half-life".

CLINICAL RESEARCH

The proof of therapeutic efficacy in the human is requested by authorities as a prerequisite for giving a marketing licence for a drug. This request is a result of the last two decades. It has been introduced in Germany in 1978 only. The spontaneous variation of illnesses from one individual to another creates many pitfalls. Anecdotal evidence is no proof; what is needed are well planned, prospective, statistically valid, controlled clinical trials. The results should be reproducible in different studies. This means careful selection criteria for patients who go into such a study. At the same time it would be desirable to generalize from the results of such studies to a large variety of conditions. However, these two requirements, reproducibility and generalisability, are largely excluding one another. For benzodiazepines efficacy has been proved since twenty years; however, clinical research is still going on in view of new questions that come up in the classical indications as well as in new indications like schistosomiasis. It is virtually impossible to find out about all aspects of a drug right up to registration (and even afterwards). So any introduction of a new drug must be a calculated risk, the calculation being based on the therapeutic advantages on one side and the adverse reactions on the other side. To find out how a drug behaves in wide application new methods have been asked for: they enter the category of

POSTMARKETING SURVEILLANCE

This is a new field, not specific to benzodiazepines, but to all drugs. Side-effect monitoring, either by spontaneous reporting by doctors of single cases or by cohort studies after introduction is only one aspect. Drug utilization studies have been asked for more and more in the last decade. The benzodiazepines have prompted questions after they have been introduced between ten and twenty years. Dependence is one of these. This problem has stirred some emotion. Some hasty decisions have been taken by some authorities on anecdotal evidence. It may be asked whether they should not better be taken on the ground of scientific, not anecdotal evidence in analogy to what holds true for giving a license for marketing a drug.

SOCIAL ASPECTS

A still newer aspect is the question of the effect of a drug in the whole social context. Cost benefit analysis is difficult enough for a drug. Several drugs have been shown to be cheap and efficient treatwent. Even more difficult is theevaluation of social effects of a drug; and the se social effects are relevant in psychotropic drugs in general and in benzodiazepine tranquilizers in particular. Among the very first of such studies two examples can be quoted that have been completed by my firm.

One study by Proctor compared the effects on workplace parameters of psychoactive versus non-psychoactive medication with special emphasis on diazepam. The available figures clearly suggest that

1. taking any medication is associated with greater absenteeism as would be expected since the sick are more likely to receive medication as to be absent, and,
2. diazepam is not associated with any difference in performance or in accident or absentee rate above that observed in patients taking any other type of medication. Results from this survey show no increased negative effects in the workplace associated with diazepam use.

The second study by Whybrow, Matlins and Greenberg, investigated the social impact of psychotropic drugs. Three drug categories had a beneficial effect on antisocial behaviour: Major tranquilizers, antidepressants and minor tranquilizers. Minor tranquilizers were most effective in ameliorating behaviour disruptive of family life: Verbal and physical abuse of family members, and neglect of family. Stimulants, barbiturates and alcohol showed distinctly less social benefits, alcohol being the worst in this study.

CONCLUSION

In the 20 years since the introduction of benzodiazepines into medical therapy, great progress has been made in several fields of research related to them. Some trends of this research have been depicted. In the same time evaluation of drug therapy has become (and is still becoming) progressively empirical. Social studies bring in a new dimension as the mere scientific methodology based on empiricism will not be sufficient. These studies involve also human value judgments. These values have to be set; they can hardly be found empirically. Here pure empiricism is no longer sufficient. The action of a drug on bodily and psychical functions may be similar in all human individuals. However human value judgments may change from one culture to another, and even within one (pluralistic) society. Here resides probably the most formidable task for the future. Scientific thought cannot remain in an ivory tower, but has to be integrated into the whole of society, involving by this process automatically human value judgments. This has been seen clearly already by Comenius who wrote 1668 about scientific progress as a basis for a better society (but not as a self-sufficient objective): "That something has been achieved and that in a glorious manner is attested by the splendid establishment of the Royal Society in London for the investigation of the mysteries of Nasure and by the publication already of so many admirable inquiries and discoveries... If you rest content with that, and do not propose to build something upon those foundations, you will deserve ridicule...and your work will be a Babylon turned upside down, building not towards hea-

ven, but towards the earth". The hope was expressed that these problems will be mastered, even if the way how to do this cannot yet be seen in all detail.

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