Abstract:
Here we describe how Adverse Drug Reactions (ADRs) can play an important role in pharmaceutical research and drug development. Not only do ADRs represent the risks and drawbacks associated with drugs but they can also be related to other knowledge available in pharmaceutical and medical research. We offer a model that can be used to systematically map the pathways through which ADRs can lead to innovative research. These pathways include chemical, therapeutic or (patho)physiological steps that can be taken to arrive at new knowledge based on ADRs.

In this chapter we present the development of the Angiotensin-Converting Enzyme inhibitors, especially Captopril, as a case study. We show that the similarity between the ADR-profiles of Captopril and Penicillamine has been a starting point for further drug innovation in this area. Historical analysis shows that in several instances research in the field of Angiotensin-Converting Enzyme inhibitors has been triggered by ADRs. The model, presented here might be applicable to other areas of innovative drug research.

Keywords:
ACE-Inhibitors, Captopril, Penicillamine, History of the 20th century, Adverse Drug Reactions, Drug Development

Introduction:
Captopril was the first drug to be introduced in the class of Angiotensin-Converting Enzyme inhibitors (ACE-inhibitors). Since 1979 it has been increasingly used for the treatment of hypertension and congestive heart failure (1,2), and more recently also for the treatment of proteinuria in diabetic patients and for post myocardial infarction therapy (3,4). The development of Captopril started in the late sixties with the recognition of the ACE-inhibiting effect of some peptides isolated from Brazilian snake (Bothrops jararaca) venom, as reviewed by Zanchetti, Ondetti and others (5,6). In 1968 Bakhl found that the bradykinin potentiating factors from the snake were competitive inhibitors of the Angiotensin-Converting Enzyme. One of these isolated factors was SQ 20881 (teprotide) that was known to lower the blood pressure satisfactorily, but only by intravenous administration (7). The lack of an oral administration route inspired the search for orally active ACE-inhibitors. In analogy to the enzyme model of carboxypeptidase A by Byers and Wolfenden, the Squibb scientists Ondetti, Cushman, and colleagues presented a three dimensional structure of ACE (8) and on the basis of molecular modelling they were able to design potential inhibitors. One of the synthesized compounds exhibited a potency which was 1000 times higher than the original peptides and was later on named Captopril (9).

The therapeutical potential of the new ACE-inhibitor at that time was not clear. The beneficial role in a number of cardiovascular diseases had still to be established (10). The idea that inhibition of ACE was useful for the treatment of hypertension was questioned in 1974 by Gross (11). However, intensive research programs went on and the clinical studies with Teprotide and Captopril showed positive results in (severe) hypertensive patients (at first renovascular, and later essential hypertension). As a consequence, the concept of ACE-inhibition became accepted as a useful intervention for the ever growing area of kidney and cardiovascular diseases (12).

In this article the particular innovations will be analyzed based on knowledge obtained from observed adverse drug reactions. We present a historical analysis of ADR-related developments in order to illustrate a model of the structural role of ADRs in medical and pharmaceutical research.

Pharmaceutical Innovation:
We use a broad concept of pharmaceutical innovation and development. Every improvement related to drugs is regarded as pharmaceutical innovation or development. This can be a change in drug use or drug formulation that is directly or indirectly of benefit for application in practice. It can also be knowledge improvement that helps to explain why and how a drug is active. Thus, any knowledge about structural and functional properties of the drug, its effectiveness, and use, is, in addition to knowledge from medical chemistry, biochemistry and pharmacology, included in this broad concept of pharmaceutical innovation.

Drug design and development is a very complex, and not always clearly structured process. Knowledge from different disciplines can be used as input for the process of developing a drug. The input may originate from practice, and from applied or basic research. There is no best way to design and develop a new drug. However, in the multi-disciplinary process some basic patterns can be recognized.

Three major pathways of development are distinguished in figure 1: a chemical, a therapeutical and a (patho)physiological one. The input for one of the three corners of the diagram can be knowledge or hypotheses for the development of a new drug. The process of drug development then continues through the other corners, or immediately results in a new drug.

In practice, a combination of the simultaneous input into two or three corners very often occurs. The pathways can be followed either in sequential order (e.g., first therapeutic, then (patho)physiological and last chemical or in different order), or in parallel order (e.g., chemical and (patho)physiological at the same time). Sometimes the pathways are the result of an intentional strategy, but this is not necessary. Furthermore, the development of a drug need not be in the hands of one research group, i.e. the several stages involved in developing a drug can be carried out by different groups or institutes.

In order to describe the possible ways in which the establishment of ADRs can influence medical research positively, we present a model of pathways and the type of products of innovations (see figure 2). The model is based on elements from the history of the ACE-inhibitors and more general literature about drug development. The model can also be used to analyze the development of drugs other than ACE-inhibitors. It will be briefly introduced in this section, and illustrated with examples taken from the history of the development of ACE-inhibitors in the subsequent sections.

The model is divided into three segments. The first is the input, i.e. information related to ADRs. The second phase is formed by the pathways which will be explained more in depth in the next section. The third phase are the possible outcomes; products, processes and
Figure 1: Disciplines influencing drug development

Pathways can be integrated in a hierarchical view of drug discovery (instead of a hierarchical model), where information from different sources can play a minor or major role in the innovative process or even no role at all (13) (see also figure 1). We focus on pathways of innovation through which ADRs influence this process. Usually ADRs are an unwanted outcome of medical innovation. For the most part, innovations resulting from observed ADRs are considered to be serendipitous or accidental (14, 15). Typical examples found in pharmaceutical literature are minoxidil (hypertension, hair growth), chlorpromazine (prevention of shock, tranquilizer and anti-emetic), amantadine (antiviral, parkinson’s disease), the use of H1 antagonists as sleeping agents. In all of these cases one of the ADRs, reported after the drug had been introduced on the market, was used as a trigger for a second indication. According to the model in figure 2 we can label the developments as being the result of the therapeutic pathway. A more complex example is the sulfonylureas for oral use as antidiabetic drugs, illustrated by a quotation from Spilker (1989):

'Adverse reactions also stimulate companies to search for chemically related compounds that have more potent actions of the desired type. A well-known example of this situation relates to the sulfonamide antibacterial drugs. It was noticed that “sulfa” drugs lowered blood sugar and caused diuresis (excessive urination) as adverse reactions. Many new compounds were synthesized over many years in an attempt to exploit these adverse reactions. Eventually, the oral antidiabetic drugs (sulfonylureas) were discovered.'

In this example the chemical and therapeutic pathway are both followed, e.g. by manipulating the chemical moiety the therapeutic effect could be directed in the desired way.

Figure 2: Model of possible pathways leading from an ADR to a new product, process, or application.

Explanation of the model: pathways of innovation
The presence of an ADR can be related to different pieces of knowledge, for example suspected chemical structures, (patho)physiological interactions, therapeutic applications. We will now continue with a more extensive description of the three pathways.

Pathway I: Chemical.
The most important source for this type of innovation is the concept Structure Activity Relationship (SAR). In some cases the ADR can be related to (a part of) the chemical structure of the therapeutic compound and this information can be used to modify or design novel chemical substances. Similarities in ADR profiles and in a chemical moiety stimulate research on eliminating this suspected moiety. Exploring such activities of chemical components can therefore lead to a broader use of certain chemical compounds. Defining the relationship between structure and activity brings the focus on interaction- or receptor-models.

Potential outcomes of pathway I:
1. Elimination of a chemical moiety from the drug molecule suspected to be related to ADRs.
2. Confirmation of hypothetical receptor model for the particular group of agents.
3. Basic research on the physiological role of specific chemical substituents, such as the sulphydryl group, in the case of the ACE-inhibitors. (SAR)

Pathway II: Therapeutic.
This pathway is often referred to as clinical serendipity (14). ADRs can provide the impulse for scanning alternative therapeutic possibilities of a drug. This may open new application areas (ADR becomes the therapeutic lead to a new indication) or provide a clearer idea on when and how the drug is of therapeutic benefit. Similarities in ADR profiles of two drugs, which themselves are therapeutic observations, stimulate research on replacing one of these drugs by the other one.

Potential outcomes of pathway II, in relation to ACE-inhibitors:

Applications.

In practice, there is no need to label the pathways in such a structured way as we do now. However, for the purpose of developing a model on the role of ADRs in innovative research, we first want to clarify what each of the pathways can look like, and how each of them can contribute to the process of drug development. Therefore we have - sometimes artificially - separated the pathways.

The examples we describe could have been presented in a much more interwoven way. This would have been closer to practice, but of less use for formulating a theoretical framework of drug development.

Pathways are deliberate or accidental steps that can be identified in scientific research which are taken in order to arrive at a new product, process or application. A pathway can be pictured as a straight line of events or be looked upon as sequential or parallel combinations of two or more pathways (as mentioned above). These
1. The dose dependency of ADRs known from related drugs can be used to change the dose regimen of the ADR causing drug.

2. Similarities in the ADR profile might stimulate research into similarities in the therapeutic profile. A new indication may arise from this.

3. Further acceptance of the particular medical concept, based on improved risk/benefit ratios.

**Pathway III: (Patho)physiological.**

The observed ADRs may direct attention to activities on certain (patho)physiological processes. Looking for an explanation of the observed adverse effect may be an important trigger for new research. Similarities in ADR profiles and chemical moiety stimulate research on the (patho)physiological role of this moiety.

Potential outcomes of pathway III, in relation to ACE-inhibitors:

1. An input to other fields of research with regard to the physiological mechanisms of the ADR.

2. The testing of new hypotheses of mechanisms of action.

In the next section examples will be given from the history of Captopril to illustrate the three separate pathways from the model described above.

**Pathway I, Chemical:**

In 1979 Captopril was used for the first time on a larger scale in clinical trials. Quite rapidly some unexpected ADRs were observed. Among these ADRs were loss of taste, rashes, oral ulcers, neutropenia, proteinuria, allergic reactions and angioneurotic oedema (16).

Some of the ADRs of Captopril proved to be reversible and/or dose-dependent. The clinical observation of these ADRs led various researchers to note the striking resemblance between the ADR profiles of Captopril and Penicillamine (17,18,19,20,21). Interestingly, these remarks can be found in articles and reviews from authors of various backgrounds, but not in the articles written by the makers of Captopril (22,23,24).

The similarities in ADR profiles of Captopril and Penicillamine were related to the similarities in the chemical structures of both drugs: the particular drugs have a thiol or sulphydryl group in common. This structural element was considered to be a logical explanation for the observed similarities in pharmacological activity as well as for some of the ADRs of Captopril (25,26,27,28,29).

In the next quotation this notion is formulated and followed by a prediction of innovation.

"Interestingly, the profile of adverse effects with Captopril bears considerable similarities to that of Penicillamine. Both drugs have certain structural similarities, including a sulphydryl group, inviting speculation on an association between these structural components and adverse effects. Although such an association does remain speculative, the development of Angiotensin-Converting Enzyme inhibitors which are devoid of a sulphydryl group will undoubtedly be awaited with interest." Heel et al in 1980 (30).

After the development of Captopril researchers were soon occupied in trying to find other ACE-inhibitors being stimulated by the interesting pharmacological profile.

Scientists specifically searched for ACE-inhibitors without sulphydryl groups. This idea had to be reconciled with the molecular model of ACE of Ondetti and Cushman, in which the sulphydryl group was supposed to play a role in the binding of the drug to the enzyme. The chemist Patchett, working for MSD, pointed out that the development of Enalapril, apart from the industrial need, was triggered by two ideas. The first was the search for a compound lacking a sulphydryl group and the second concerned the data on structure activity relationship that were available from Captopril and some of its derivates (31). The design and development of Enalapril proved to be very successful and was conceived as a logical result of the introduction of Captopril (32). This is illustrated by the following quotation from Soudijn 1982 (33):

"...This (SAR, FR, RV) led to the development of a series of non-mercapto ACE-inhibitors derived from Captopril. One of them, Enalapril, a potent ACE-Inhibitor with a long duration of antihypertensive action, is now tested in clinical trials."

This innovation was successful because Enalapril is an effective drug and it does not show the ADRs that were thought typical of the sulphydryl group containing ACE-inhibitor, Captopril. Based on the hypothetical enzyme model of Ondetti and Cushman, the sulphydryl group was replaced by a carbonyl compound. The higher potency and increased binding of Enalapril to ACE compared to Captopril lend support to the hypothetical model of the enzyme. Consequently the enzyme model could be used for subsequent research with less uncertainty.

Another development arose from a closer investigation of the suspected sulphydryl group. Structure Activity Relationship studies of sulphydryl groups as attached to other molecules, in relation to the spectrum of unwanted activities were performed. Captopril is described as a typical sulphydryl containing drug in articles on this subject (34,35,36,37), rather than as an ACE-inhibitor.

**Pathway II, Therapeutic:**

One of the problems in the clinical use of Captopril was the establishment of a narrow therapeutic window (38,39,40). Plasma levels of Captopril didn’t prove to be proper indicators of the pharmacological and toxicological activity. In the case of Penicillamine, which had been on the market much longer, it was known that the ADRs typical of sulphydryl containing compounds were dose-dependent (41).

This knowledge could be used as an analogy for Captopril. Clinical trials with a lower dose showed that this dose regimen could be used without loss of antihypertensive activity. This led to a marked improvement of the therapeutic safety profile of Captopril (42).

Another consequence of the improved chemical and therapeutic understanding of the ADRs was a higher level of acceptance of the concept of ACE-inhibition. Instead of the negative effects in the first years, the effective and safe treatment at lower doses was the decisive factor in the acceptance of the therapeutic principle of ACE-inhibition. The ADRs were an invitation to change the risk-benefit ratio rather than a dead end for this concept.

Another direction that was taken was the research on alternative effects of both drugs. In the following quotation a clear statement is made about the potential of Captopril. Quotation Martin et al 1984 (43):

"A number of features indicate the potential of Captopril for treating rheumatoid arthritis (RA). Firstly, the molecular structure is similar to that of penicillamine-an acid group (-COOH) at one end of the molecule is separated by a short chain of carbon atoms from a sulphydryl group (-SH) at the other end. Secondly, both compounds bind copper. Thirdly, the two drugs produce similar side effects. These features invite speculation not only on the association between their structural components and adverse effects but also on the potential of Captopril as an effective treatment for RA.

Thus, on the basis of similarities in ADR profiles, a relationship was assumed between other potentially beneficial actions of the
particular drugs. It was hypothesized that the sulphhydryl group might play a role in the positive effect of Penicillamine in the treatment of rheumatoid arthritis. Here the emphasis is not on negative effects of the drugs that should be avoided, but rather on the positive effects that both drugs might have in common (34,35,44).

In the article by Martin et al, from which the quotation was taken, a study is described in which Captopril was tested for its activity as an anti-rheumatic drug. The authors concluded that the benefit/risk ratio of Captopril in rheumatoid arthritis seems to be good. Consequently, Captopril was considered to be of potential interest for the treatment of rheumatoid arthritis. Nevertheless the authors stated that more clinical research is necessary (43). This was not the first article in which the relation between RA and Captopril was suggested although it was the first clinical trial with this indication (45,46).

In 1986 another article about this subject was published, in which the ADRs of sulphhydryl compounds were compared (36). The ADRs are clearly mentioned as a reason why Captopril had been given to patients suffering from rheumatoid arthritis, and one other study presenting positive results was discussed (47). In a study in 1984 (47), patients suffering from rheumatoid arthritis were treated with Enalapril. In this case no beneficial effects on the disease were observed. The conclusion was drawn that the positive effects of Captopril are a result of the presence of a sulphhydryl group and not due to the inhibition of ACE. It was speculated that the sulphphydryl group might play a role in catching free radicals that produce and maintain the inflammation process. If the positive effect of Captopril on RA had been induced by ACE inhibition, it would obviously have meant a major therapeutical innovation. However, there was still discussion about a possible role of ACE in rheumatoid arthritis (48). This item was studied again in 1990 by Bird et al (49). Captopril and Pentopril were both used for the treatment of RA patients. According to the authors there is no doubt about the activity of Captopril. However, the results also show that Pentopril, an ACE-inhibitor without sulphhydryl group, is not effective in this indication (49). In the period of 1984 to 1990, there was no real change in ideas concerning Captopril as an anti-RA drug. The development process is still in an early stage. Findings are not completely certain and more research has been suggested (50). The major reason for introducing Captopril as an anti-RA drug would be the fact that its ADRs are much milder than those of comparable drugs such as Penicillamine and gold-derivates. At this moment Penicillamine is still prescribed for rheumatoid arthritis notwithstanding its severe ADRs.

Pathway III, (Patho)physiological:
Some researchers investigated the mechanisms of ADRs related to the sulphhydryl group (51,36), especially the ADRs in the field of autoimmune reactions, which were compared for Captopril and Penicillamine (52,53). One of these ADRs is a pemphigus-like skin reaction, which is found with all known sulphhydryl containing compounds in a form distinguishable from the spontaneous disease. Others are neutropenia, taste abnormalities, rash, pruritus, oral ulcers and membranous nephropathy. There is no proof that these ADRs are interrelatered (37). The goal of this kind of research seems to be to determine the full range of physiological actions caused by sulphhydryl compounds.

In the cardiovascular field, the possible role of the sulphhydryl group in the protection of the heart against reperfusion injury is still open to question. In this respect sulphhydryl groups might behave as recyclable free radical scavengers (54). The importance of this statement is that it invites studies to discriminate between the ACE-Inhibitors that are on the market at present. A problem with ADRs as a source of information is that our conception must change. An ADR is not only and exclusively a negative effect. This in contrast to the expectations of the inventors of Captopril (Ondetti, Cushman and others). They seem to consider ADRs as effects that do not fit in their view of a rationally designed drug. In this respect the following quotation of Cushman et al 1979 (55) is interesting: 'Untoward side effects and low therapeutic ratios of drugs are not necessary evils, but often result from the random manner in which a drug has been discovered. Captopril, whatever limitations it may prove to have, has been selected by a rational process of chemical design for an optimal combination of simplicity of structure, great potency, and maximal specificity for its receptor, the active site of Angiotensin I Converting Enzyme. Since this target enzyme is not essential for most normal body functions, a potent and specific inhibitor such as Captopril might be expected to have an excellent margin of safety and relative freedom from side effects when studied in the clinic as an antihypertensive drug.'

The context in which the drug is studied is indeed important for the evaluations and the implications of the observed facts. It is no coincidence that all articles that describe Captopril as a possible agent for the treatment of RA originate from a rheumatic background, although the drug was known as a cardiovascular agent. Captopril is seen as a new possibility, with relatively fewer ADRs to be used for a disease for which the existing drugs are far from ideal. This is in contrast to the articles from the cardiovascular field where the similarities between Captopril and Penicillamine are mentioned incidentally and then only with regard to the ADR profile and the structure of both drugs.

Conclusion: The negative connotation of an ADR can be a major hurdle in the process of drug innovation. Yet the examples described in this article show that ADRs can form a very stimulating impulse to innovative research. The concept of rational drug design becomes more complex in our model through combination of possible pathways. Especially the current idea of the major aspects of drug innovation, such as receptor knowledge, SAR, molecular mechanisms of action and genetics, deserves a more balanced approach. This approach can
be justified by the unexpected way in which other influences than those intended may affect the innovation process (56). The ADR-therapeutic lead model we described is a tool to structure information that can be used as feed back for the innovative process. In an article from 1989 (57) Blumenthal describes the potential of ADR-databases in finding new indications for old drugs. However, he doesn’t provide a method for deriving this information from these databases. Our model, in combination with computational linguistic techniques, can provide a tool suitable for obtaining new information from existing data. Thorough analysis of medical and pharmaceutical literature can be used in order to relate ADRs to effects and to knowledge from other disciplines. These new relations can be used as input for innovative studies.

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