BIOLOGICAL CONSEQUENCES OF DRUG SULPHOXIDATION

S.C. Mitchell
Department of Pharmacology and Toxicology
St. Mary's Hospital Medical School
Paddington, London W2 1 PG, U.K.

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SUMMARY

The addition of an oxygen atom to the sulphur centre of a compound, with the formation of a polarized S-O moiety, alters the physical and chemical properties of the molecule and can profoundly influence its biological activity, its disposition within the body and its potential fate. Examples are given to illustrate these points.

I. INTRODUCTION

Although sulphoxidation has only recently been demonstrated to occur with sulphur-containing xenobiotics /1/, it has become established and accepted as an important pathway in the biotransformation of such compounds. The formation of a sulphoxide metabolite from a sulphide may not only enhance the elimination prospects of the compound but may also alter the biological properties of that molecule.

The aim of this short review is to establish that sulphoxidation may alter the biological activity of a molecule and to attempt to explain such behaviour in terms of the nature of the sulphoxide moiety and its influence on the disposition and fate of the compound.

II. NATURE OF THE SULPHUR-OXYGEN BOND

Any differences in biological properties existing between sulphoxides and their corresponding sulphides must be a consequence of the presence of an oxygen atom chemically bonded to the sulphur.

Discussion regarding the absolute nature of the S-O bond has been continuing for many decades with opinion tending to favour either a double-bonded (I) or a single-bonded (II) situation.

$$\underset{\textbf{(I)}}{S = O} \qquad\qquad \underset{\textbf{(II)}}{S^{+} - O^{-}}$$

The bonded sulphur rarely exists in isolation and when the other substituents attached to the sulphur are sufficiently electronegative to raise the effective electronegativity of the sulphur relative to the oxygen, equal sharing of the bonding electrons should be approximated giving rise to a "double-bond" character (I). The "single-bond" situation (II) is approached with a decreasing electronegativity of the ligands, the bond becoming more polar with the π-electrons effectively residing on the oxygen atom.

The accumulation of data from many compounds regarding S-O bond lengths, either measured directly or from their related I.R. stretching frequencies, has helped to reconcile such apparently

divergent opinions regarding these two extreme bond forms and led to the view that the S-O bond may be of variable character. Such S-O bond lengths appear to range from 1.66 A (SF_5OOSF_5), a near pure "single-bond" through virtually all the intermediate values to 1.405 A (SOF_4), a near pure "double-bond" /2,3/. The possibility of overlap between the 2p orbitals of oxygen and the 3d orbitals of sulphur exists and the variable nature of S-O bonds when compounds are compared can be rationalized in terms of such orbital hybridizations.

The relatively diffuse, shallow, character of pure d-orbitals has been predicted to diminish when electronegative substituents are present which increase the electron deficiency of the bonding sulphur. As a consequence the capacity of 2p-3d orbital overlap should be strengthened /4/. This capacity for overlap will vary from one series of S-O containing compounds to another, and within a series depending upon the nature of the substituents and certain physical situations. Indeed, chemical alteration of a compound through metabolism will presumably alter the nature of an adjoining S-O bond.

Bulky substituents attached to, or close to, the sulphur, and those capable of resonance and/or producing inductive effects will modify the nature of the S-O bond, usually tending to increase charge separation. The S-O bond of virtually all organic sulphoxides, especially those with bulky aromatic substituents, will therefore tend to have some degree of polarization.

III. ALTERATION OF BIOLOGICAL ACTIVITY

A few instances have been cited within the literature where it is known that the addition of such a polarized S-O bond to a molecule clearly alters its biological activity. The full impact of this phenomenon on compounds which may potentially undergo conversion to sulphoxides is unknown and its importance is rarely appreciated.

3.1 Decrease In Activity

Chlorpromazine ring sulphoxide is virtually devoid of activity when compared to the parent phenothiazine derivative, chlor-

promazine, a potent and widely used antipsychotic agent /5/. The conversion of cimetidine, a histamine H2-receptor antagonist, to its sulphoxide yields a compound with reduced activity /6/. The sulphoxide-containing drugs, sulindac (a non-steroidal anti-inflammatory) and sulphinpyrazone (a uricosuric drug) are administered in their relatively inactive sulphoxide forms to undergo bioactivation by sulphoxide reduction. Reoxidation of these sulphides back to their original sulphoxide forms presumably decreases their activity /7/.

3.2 **Increase In Activity**

The side-chain sulphoxide (mesoridazine) and side-chain sulphone (sulphoridazine) of the phenothiazine antipsychotic, thioridazine, have significant antipsychotic activity in man which may even supercede that of the parent sulphide /8/. Thioacetamide and thiobenzamide sulphoxides have been shown to be more hepatotoxic, on a molar basis, than their corresponding sulphides and it is believed that toxicity arises by metabolism through the sulphoxide to an unstable disulphoxide which then undergoes rearrangement with subsequent covalent binding resulting in macromolecular disruption /9/. Finally, methylcysteine, an amino acid derivative, is itself fairly harmless but methylcysteine sulphoxide ("kale anaemia factor") has been implicated in the production of the severe blood disorders observed in cattle feeding on kale products /10/.

These few examples serve to illustrate the point that the conversion of a sulphide to its corresponding sulphoxide may be far from a trivial matter and may lead to an important increase or decrease in the biological activity (pharmacological and/or toxicological) of that molecule.

IV. BIOLOGICAL CONSEQUENCES OF SULPHOXIDATION

The reasons for such alterations in activity are only partially understood but the addition of oxygen to the sulphur moiety clearly alters the chemical and hence the physical and biological properties of the molecule. This alteration bestows upon the molecule apparently diverse behaviour.

Chlorpromazine is thought to exert its pharmacological effects by interaction with dopamine receptors in the brain. It has been suggested that one of the rings of the chlorpromazine nucleus, the "a" ring containing the chlorine substituent, and the dimethyl-aminopropyl side-chain interact with dopamine-related sites in the same manner as dopamine itself. In this configuration the sulphur atom of the thiazine nucleus would occupy the same position as the 3-(meta)-hydroxyl group of dopamine, probably a binding site. The formation of a ring sulphoxide would therefore presumably interfere with this binding /11,12/. Other factors, such as a change in lipid solubility with consequent alteration in distribution pattern and potential access to receptor sites must also be borne in mind.

In both man and guinea pig an oral dose of cimetidine has been shown to be almost totally excreted from the body within three days /6,13/ whereas only half of an oral dose of cimetidine sulphoxide could be accounted for during the same period /14,15/. Further work on guinea pigs has shown that this retention was dependent upon the oral route of administration and that radioactivity associated with the fifty percent of the cimetidine sulphoxide dose retained within these animals was present in the mesenteric and omental tissues /15/. The addition of an oxygen to the sulphur moiety of the cimetidine molecule profoundly influences its passage from the gut lumen to the systemic circulation.

Finally, it is generally accepted that a compound has to be above a certain molecular weight for significant amounts (above 10%) of that compound to be excreted in the bile. In rats this "molecular weight threshold" is 325+50 /16/. However, when radiolabelled dipropyl sulphide, dipropyl sulphoxide or dipropyl sulphone were orally administered to rats some 25-30% of the radioactivity was excreted in the bile over the next three days. Only dipropyl sulphoxide (m.w. 134) and smaller amounts of the sulphone (m.w. 150) were found, no sulphide being present. Despite these oxides having molecular weights less than half the required value they appeared in the bile in substantial amounts, a biological property not possessed by the corresponding sulphide /17/.

Owing to charge separation around the S-O moiety it is probable that these molecules interact more strongly with the protein and lipid environments through which they travel when compared to the corresponding sulphides. Such interactions could be as a result of the participation of the oxygen terminal of the sulphoxide group in

hydrogen bonding /18,19/. At areas of high local concentration, perhaps at excretory sites, the sulphoxides may even associate with themselves into "clusters" or "stacks" /19/ thereby temporarily increasing their molecular weight.

Evidently, a sulphoxide metabolite should not be dismissed simply as an oxide of the parent compound but should be respected as possessing unique pharmacodynamic and pharmacokinetic properties which are not predictable from a knowledge of the parent sulphide.

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