Metabolic activation of some antibacterial sulphonamides in liver

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Abstract: *Compounds causing injury to liver are known as hepatotoxins. Some of these compounds will cause toxic effects in any individual exposed to the compound beyond a certain dose. This is usually the consequence of a specific action of the molecule on the hepatocyte causing alterations or malfunction of the cell substructures and biomolecules. Antibacterial sulphonamides are first effective chemotherapeutic agents used for bacterial infection in humans. Sulphonamides are considered as derivatives of para amino benzene sulphonamide. The aim of this work was to predict the possible metabolites of some antibacterial sulphonamides in liver and their protein and DNA binding by a specialized software.*

Key words: *antibacterial sulphonamides, liver, metabolites*

INTRODUCTION

The sulphonamides represent a large class of antibiotics that have multiple clinical uses. The sulphonamides were the first effective antibiotics to be introduced into clinical medicine and have been in use continuously since the 1930's. They are considered bacteriostatic and appear to act by inhibition of bacterial biosynthesis of folic acid, which is needed for cell growth, at least in those bacteria that are sensitive to sulphonamides. Because humans rely upon dietary folic acid, they are usually resistant to the adverse effects of inhibition of folate synthesis. Sulphonamides have a wide range of antimicrobial activity against both gram-positive and –negative organisms. Unfortunately, bacterial resistance to sulphonamides is now common, and their use has decreased with the introduction of more potent classes of antibiotics [2].

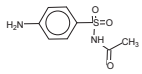
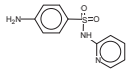
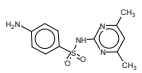
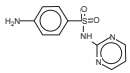
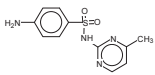
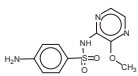
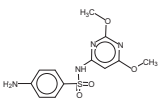
The sulphonamides are well known to cause idiosyncratic liver injury. Hepatotoxicity appears to be a class-effect, in that virtually all sulphonamides used today have been linked to rare, but convincing cases of drug-induced liver injury. The pattern of injury is variable, often mixed but it can be either hepatocellular or cholestatic. Most typically, the injury appears precipitously within one to three weeks of starting therapy, often preceded or accompanied by signs of hypersensitivity such as fever, rash, facial edema, lymphadenopathy, arthralgias, and eosinophilia or atypical lymphocytosis (or both). Hepatotoxicity from sulphonamides may represent a part of a spectrum of hypersensitivity due to sulfa-derived medications. The severity of injury varies widely. Most instances of sulphonamide related liver injury are mild to moderate in severity and self-limited in course. Importantly, sulphonamides can cause acute liver failure, particularly in instances with a precipitious onset and hepatocellular pattern of serum enzyme elevations. Indeed, the sulphonamides remain one of the most common causes of drug-induced acute liver failure [2].

The aim of this work was to predict the possible metabolites of some antibacterial sulphonamides in liver and their protein and DNA binding by a specialized software.

MATERIALS AND METHODS

Compounds. Some antibacterial sulphonamides [1] were investigated which are presented in Tables 1 and 2.

Table 1 CAS number, Name, structure of compound and therapeutic uses of some antibacterial sulphonamides

№	CAS number	Name of compound	Therapeutic uses	Structure of compound
1	144-80-9	N-((p-Amino phenyl)sulfonyl) acetamide	Ophthalmologic use	
2	144-83-2	4-Amino-N-2-pyridinyl-benzenesulfonamide	Dermatitis herptiformis	
3	57-68-1	4-Amino-N-(4,6-dimethyl-2-pyri midinyl)- benzene sulfonamide	Used in meningitis	
4	68-35-9	4-Amino-N-2-pyrimidinyl- benzene sulfonamide	Used in meningitis and nocardiosis	
5	127-79-7	4-Amino-N-(4-me thyl-2-pyrimidinyl)-benzenesulfonamide	Systemic sulphonamides	
6	152-47-6	4-Amino-N-(3-me thoxypyrazinyl)-benzenesulfonamide	Chronic bronchitis, respiratory tract infection	
7	122-11-2	4-amino-N-(2,6-dime thoxy-4-pyrimidinyl)-benzenesulfonamide	Systemic sulphonamides	

OECD (Q)SAR Application Toolbox. (Quantitative) Structure-Activity Relationships [(Q)SARs] are methods for estimating properties of a chemical from its molecular structure

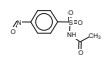
and have the potential to provide information on the hazards of chemicals, while reducing time, monetary costs and animal testing currently needed. To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the OECD (Q)SAR project has developed various outcomes such as the principles for the validation of (Q)SAR models, guidance documents as well as the QSAR Toolbox [4].

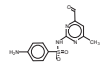
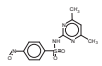
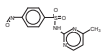
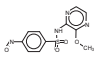
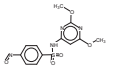
Metabolic pathways documented for 200 organic chemicals in different mammals are stored in a database format that allows easy computer-aided access to the metabolism information. The collection includes chemicals of different classes, with variety of functionalities such aliphatic hydrocarbons, alicyclic rings, furans, halogenated hydrocarbons, aromatic hydrocarbons and haloaromatics, amines, nitro-derivatives, and multifunctional compounds. *In vivo* and *in vitro* (predominantly, with liver microsomes as experimental systems) studies were used to analyze the metabolic fate of chemicals. Different sources, including monographs, scientific articles and public websites were used to compile the database [3, 4].

RESULTS AND DISCUSSION

The results of the probable metabolic activation in liver (observed and predicted) of some antibacterial sulphonamides are presented in Table 2.

Table 2 Probable metabolic activation of some antibacterial sulphonamides by (Q)SAR Application Toolbox

№	Antibacterial sulphonamides	Observed liver metabolism by Toolbox	Liver Metabolism Simulator by Toolbox
1	N-((p-Amino phenyl)sulfonyl) acetamide	0 metabolites;	7 metabolites (two of them are active metabolites);   1) 2) Protein binding – Nitroso protein binding; DNA binding – Nitroso compounds;
2	4-Amino-N-2-pyri dinyl- benzene sulfonamide	0 metabolites;	7 metabolites (three of them are active metabolites);   1) 2)  3) Protein binding – Michael-type nucleophilic addition and Nitroso protein binding; DNA binding – No binding;
3	4-Amino-N-(4,6-di methyl-2-pyri midinyl)- benzene	0 metabolites;	6 metabolites (two of them are active metabolites);

	sulfonamide		  1) 2) Protein binding – Schiff base formation and Nitroso protein binding; DNA binding – No binding;
4	4-Amino-N-2-pyrimidinyl- benzenesulfonamide	0 metabolites;	3 metabolites (one of them is active metabolite);  1) Protein binding –Nitroso protein binding; DNA binding – No binding;
5	4-Amino-N-(4-methyl-2-pyrimidinyl)- benzene sulfonamide	0 metabolites;	6 metabolites (two of them are active metabolites);   1) 2) Protein binding – Schiff base formation and Nitroso protein binding; DNA binding – No binding;
6	4-Amino-N-(3-methoxypyrazinyl)- benzenesulfonamide	0 metabolites;	7 metabolites (two of them are active metabolites);  1) 2) Protein binding – Schiff base formation and Nitroso protein binding; DNA binding – No binding;
7	4-amino-N-(2,6-dimethoxy-4-pyrimidinyl)- benzene sulfonamide	0 metabolites;	12 metabolites (two of them are active metabolites);  1) 2) Protein binding – Schiff base formation and Nitroso protein binding; DNA binding – No binding;

CONCLUSIONS

Drug-induced hepatotoxicity will remain a problem that carries both clinical and regulatory significance as long as new drugs continue to enter the market. Unfortunately, recognizing toxicity of specific drugs is limited by the relatively rare overall incidence of hepatotoxicity as well as underreporting. Observed and predicted liver metabolites of some sulphonamides were predicted by a software ((Q)SAR Application Toolbox. The protein and DNA binding of the metabolites of the antibacterial sulphonamides was estimated.

REFERENCES

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