chain, as do phenobarbital and a great number of other drugs[13, 21, 26]. The only difference is that these drugs are thought to enter the liver cell and to react with the microsomal systems[21, 26], whilst the anion exchanger resin does not because it is not absorbed by the intestine.
The activities of the soluble NADPH-generating enzymes, glucose 6-phosphate dehydrogenase and malic enzyme, are increased. This fits well with the greater demand for NADPH in order to feed the microsomal hydroxylation reactions. Malic enzyme is also increased with aryloxyalcanoic acids[24, 25]. Treatment of rats with 13 437-Su results in liver enlargement and increased activities of alkaline phosphatase, catalase, malic enzyme, aminopyrine demethylase, and microsomal cytochrome c and neotetrazolium reductases (Kief and Beyhl, unpublished results[24, 25]).

Dowex 1 x 2 treatment combines the effect of the aryloxyalcanoic acids (clofibrate-like drugs) and the microsomal inducers (phenobarbital-like drugs). It seems as if part of the effects of the aryloxyalcanoic acids can be ascribed to an interference with bile acid enterohepatic circulation (inhibition of enteral bile acid reabsorption, e.g.). On the other hand, induction of microsomal drug-metabolizing enzymes may be due to an overcome of bile acid negative feedback control of enzyme synthesis brought about by the inducing agent. So it is not necessary that a microsomal inducer should enter the liver cell; it can achieve its inducing action also by an indirect way, namely sequestration of bile acids in the intestinal tract.

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## Improved treatment of organophosphate intoxication by use of scopolamine or dexetimide[1]

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*Summary.* Organophosphate intoxications have been treated by dexetimide plus obidoxime. Rabbits intoxicated by the 50–80fold $LD_{50}$ of different organophosphates survived. Prophylactic application of dexetimide or scopolamine plus obidoxime increased the $LD_{50}$ of DFP by a factor up to 180.

It is generally recommended to treat an intoxication with organophosphates – widely used as insecticides and in stock as chemical warfare agents – by repeated administrations of high doses of atropine. The treatment might be improved by the additional application of enzyme reactivators of the oxime type, e.g. pralidoxime and obidoxime. This treatment has to be supplemented by symptomatic procedures[2]. This commonly proposed therapeutic scheme often fails to be successful. The lack of success might be caused by the relative inability of atropine to counteract the intoxication of the central nervous system. We, therefore, directed our attention to cholinolytic drugs which more readily penetrate the blood-brain-barrier. The preliminary results obtained with scopolamine and dexetimide, a drug displaying strong central anticholinergic activity[3], will be reported. Dexetimide is the biologically active enantiomer of benzetimide (Tremblex®).
In a first series of experiments, the protective potency of dexetimide and of dexetimide plus reactivator was compared with that of atropine and scopolamine. Diisopropylphosphorofluoridate (DFP) was injected s.c. to mice (NMRI, 17–23 g b.wt) in a dose range of 24–4400 μmoles/kg b.wt. The $LD_{50}$ amounted to 24 ± 0.14 μmoles/kg b.wt under control conditions. As shown in table 1, neither the cholinolytic drug nor obidoxime alone displayed a significant protection. The combined prophylactic treatment by atropine plus obidoxime resulted in a protection factor of 28 which is in accordance with other reports[4, 5]. An increase of the atropine dosage did not yield higher protection. Replacing atropine by the stronger centrally acting drugs scopolamine or dexetimide proved to result in far superior protection, as demonstrated by the protective factors of 183 and 180, respectively. In regard to scopola-

Table 1. Toxicity ($LD_{50}$) of DFP in mice after pretreatment by cholinolytics and obidoxime

| μmoles/kg b.wt | Obidoxime (mol.wt 359) μmoles/kg b.wt | $LD_{50}$ DFP (mol.wt 184) μmoles/kg b.wt | Protection factor* |
|---|---|---|---|
| Atropine (mol.wt 347) | | | |
| 20 | – | 45 | 1.9 |
| 10 | 10 | 280 | 12 |
| 10 | 100 | 680 | 28 |
| Scopolamine (mol.wt 384) | | | |
| 20 | – | 42 | 1.8 |
| 10 | 10 | 610 | 25 |
| 10 | 100 | 4400 | 183 |
| Dexetimide (mol.wt 399) | | | |
| 20 | – | 38 | 1.68 |
| 10 | 10 | 960 | 40 |
| 10 | 100 | 4360 | 180 |
| – | 10 | 44 | 1.7 |
| | 100 | 62 | 2.3 |

The $LD_{50}$ in controls was 24 μmoles ± 0.14/kg b.wt. The drugs were applied s.c., the protecting compounds were injected 15 min before DFP administration.

*Protection factor = $\frac{LD_{50}\ \text{pretreatment}}{LD_{50}\ \text{controls}}$.

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Table 2. Therapeutic efficiency of dexetimide plus obidoxime in treating organophosphate intoxications of rabbits

| Organophosphate | Number of animals | $LD_{50}$ mg/kg b.wt (controls) | Dose range of organophosphates mg/kg b.wt* | Dose range of dexetimite mg/kg b.wt | Dose range of obidoxime mg/kg b.wt | Therapeutic factor |
|---|---|---|---|---|---|---|
| Paraoxone s.c. | 11 | 0.4 | 2.0 –24 | 0.8– 8.0 | 7.2 | 60 |
| Paraoxone i.v. | 10 | 0.3 | 0.45–15 | 8.0–16 | 3.6–7.2 | 50 |
| DFP s.c. | 7 | 1.0 | 40 –80 | 0.8– 8.0 | 7.2 | 80 |
| OMPA i.v. | 5 | – | 10 –40 | All animals died in spite of treatment | | |

The therapeutic factor has been calculated from the highest dose of organophosphate which could be overcome by the antidotes i.v. injected at the onset of intoxication (therapeutic factor $= \left(\frac{\text{dose of organophosphate}}{LD_{50} \text{ controls}}\right)$.

The $LD_{50}$ values were taken from literature (Wescoe et al.[6], Karlog[7]) and their applicability to our animal batch was checked. * Dose range which was survived by the combined treatment.

mine, this result is supported by the reports of other authors[6,7]. Because of the risk for the experimentators of becoming intoxicated, it was not possible to determine the protective potency of scopolamine or dexetimide against still higher doses of DFP.

In a second series of experiments, the therapeutic potency of dexetimide plus obidoxime was investigated in rabbits poisoned with organophosphates. For the sake of comparison with atropine, and for checking the $LD_{50}$-values, a total of 82 rabbits (hybrids, 1900–3500 g) were poisoned with organophosphates. The organophosphates diethyl-paranitrophenylphosphate (paraoxone), DFP and octa-methyl-pyrophosphoramide (OMPA) were applied to rabbits i.v. or s.c. Dexetimide plus obidoxime were given i.v. as soon as the intoxication became evident. The therapy was regarded successful when the animals survived at least 72 h after application of the poison. When treated with 20 or 40 μmoles dexetimide/kg b.wt plus 20 μmoles obidoxime/kg b.wt, the animals survived 60 times the $LD_{50}$ of DFP s.c., 50 times the $LD_{50}$ of paraoxon i.v., and 80 times the $LD_{50}$ of paraoxone s.c. (see table 2). An intoxication by OMPA which is considered to act entirely peripherally could not be influenced by the therapeutic procedure. In contrast to the repeated application of atropine, necessary for the treatment of organophosphate intoxication, one single application of dexetimide proved to be sufficient to overcome the intoxication completely. The results of our animal experiments demonstrate that the combination of dexetimide and obidoxime is superior to the combination of atropine and obidoxime recommended for the therapy of organophosphate intoxication in man.

In consequence of the results reported here we suggest the use of dexetimide or scopolamine in the treatment of organophosphate intoxication to improve the rate of recovery. Dexetimide is used for treatment of parkinsonism, and is commercially available in some European countries.

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## Candletoxins A and B, 2 new aromatic esters of 12-deoxy-16-hydroxy-phorbol, from the irritant latex of Euphorbia poisonii Pax.

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*Summary.* 2 new aromatic esters of 12-deoxy-16-hydroxy-phorbol, known as candletoxins A and B, were isolated from the irritant latex of Euphorbia poisonii Pax. Compound A was identified as 12-deoxy-phorbol-13-O-phenylacetate-16-O-α-methyl-butyrate-20-acetate, and compound B was the C-20 desacetyl analogue.

Euphorbia poisonii Pax. latex was collected by one of us in West Africa and has been shown to produce acute inflammation of mice ears[2]. From the ether fraction of the extract, biologically active esters of 12-deoxyphorbol and resiniferol[3–5] were isolated together with 2 minor compounds which we propose to call candletoxins A and B. Both of these toxins are aromatic esters of 12-deoxy-16-hydroxy-phorbol. This tigliane derivative was initially isolated from E. cooperi[6] where it occurred naturally in

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