POSTER COMMUNICATIONS

The information content of pharmacological experiments

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The information yield of experiments can be found in terms of their negative entropy, given that the experimental result can be expressed in terms of probabilities (Shannon, 1948).

The responses of tissues in pharmacological work are a function of probabilities (e.g. the probability of open channels, 'P_{open}',) but the precise nature of the function is not known. However, there are grounds for thinking that it must be fairly direct (Colquhoun, 1973). It is therefore reasonable to work out the information yield for a set of assumed values for 'P_{open}', using the binomial assumption that each channel exists in only one of two conformations (open or shut). The information is then found to be

$$H_n = -\sum_{k=1}^{n} P_k \log_2 P_k$$

where H_n is the information gained from n channels, and P_k is the probability of any particular outcome of the experiment in the n channels (Guiasu, 1977).

This calculation shows that, for small groups of channels the information yield rises to a shallow peak at the mid-point of the curve. This is not surprising since the function is symmetrical, but the shapes of the curves, which will be demonstrated, are of some interest in considering the use of dose response curves in pharmacological practice. The results provide added justification for the usual practice of taking the ED_{50} in pharmacological measurements.

References

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Identification of two sulphur containing urinary metabolites of cinnamic aldehyde in the rat

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Cinnamic aldehyde is a widely used flavouring agent and a well-known contact sensitizer.

Because this substance has been reported to produce a glutathione depletion in the liver (Boyland & Chasseaud, 1970) we investigated its metabolism.

After i.p. administration of cinnamic aldehyde (3.8 mmol/kg in arachis oil) in the rat ($n = 4$) the urinary thioether excretion amounted to (6.5 ± 1.0)% of the dose. Two sulphur containing metabolites were isolated and identified by synthesis, n.m.r., and mass spectrography as 3-S-(*N*-acetylcysteinyl)-3-phenyl propylalcohol and 3-S-(*N*-acetylcysteinyl)-3-phenyl propionic acid.

Reference

BOYLAND, E. & CHASSEAUD, L.F. (1970). The effect of some carbonyl compounds on rat liver glutathione levels. *Biochem. Pharmac.*, **19**, 1526–1528.

Metabolism and toxicity of acrylates and methacrylates

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In addition to being very toxic to the skin acrylic and methacrylic esters have a strong contact sensitising capacity. An increasing use of these substances in many fields is a problem in occupational medicine and dermatology. Occlusive application of methyl acrylate on the shaved guineapig skin produced, like in man, a bullous erythema, histologically characterised by a spongiosis deep in the dermis. Autoradiography showed that metabolism of a locally administered dose was practically limited to the skin in the first 24 h; radioactive material was transported by the blood to the kidneys and concentrated in the

bladder whereas other organs showed a slowly rising concentration. After an i.p. dose the liver was the target organ: 35% of the dose (0.29 mmol/kg, $n = 3$) was excreted as CO_2 by the lungs in the first 8 h after injection, 40% in the first 72 hours.

After local application no thioether excretion was found in the urine in the first 24 h, 2% of the dose in the second 24 hours. Systemic administration resulted in a urinary thioetherexcretion of 6% of the dose in the first 24 h, 1% in the second 24 hours. Metabolism was studied further in the rat and in isolated rat liver.

A decreasing thioether excretion and glutathione depletion in the liver was found in the application of acrylic esters of alcohols with increasing chain lengths. A simultaneous administration of the esterase inhibitor TOTP showed a dramatic rise in thioether excretion both with methyl acrylate (0.7 mmol/kg, from 4.3% to 27.4% of the dose) and methyl methacrylate (0.85 mmol/kg, from 0.55% to 12.1% of the dose).

Mercapturic acids were isolated and identified as β-S-(*N*-acetylcysteinyl)propionic acid from acrylate and β-S-(*N*-acetylcysteinyl)isobutyric acid from methacrylate.

The quantitative analysis of 6-keto $PGF_{1\alpha}$ in biological fluids by stable isotope dilution utilizing gas chromatography–mass spectrometry (GC–MS)

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Prostacyclin (PGI_2) a potent anti-aggregatory and vasodilator prostanoid is chemically hydrolysed to 6-keto $PGF_{1\alpha}$, a substance which has been isolated from numerous biological systems (Moncada & Vane, 1979). We have developed a GC–MS assay for 6-keto $PGF_{1\alpha}$ to quantify its synthesis in cardiovascular and pulmonary systems.

Plasma (15–20 ml) or lung perfusate (50 ml) is equilibrated with 3,3,4,4 tetradeutero 6-keto $PGF_{1\alpha}$ (25 ng). After acidification to pH 3 samples are applied to 10 ml volume XAD-2 columns and successively eluted with 15 ml of distilled water and 5 ml of *n*-heptane. Prostanoids are eluted with 10 ml methanol, collected in test tubes and the methanol evaporated under nitrogen. The vacuum dried residues are subjected to thin layer chromatography using the FVI solvent (Anderson, 1969). Zones corresponding to authentic 6-keto $PGF_{1\alpha}$ are scraped from the plates, eluted twice with methanol which is evaporated to dryness. Organic residues are redissolved in 1.0 ml borate buffer (pH 8.5) and extracted with ethyl acetate (2.5 ml) which is discarded. The aqueous phase is reacidified to pH 3 and extracted with fresh ethyl acetate (2.5 ml). The ethyl acetate is evaporated under nitrogen and the residues converted to *O*-methyloxime, methyl ester, trimethylsilyl ether derivatives as described previously (Black, *et al.*, 1978). From the final solution (25 µl) 2 × 10 µl aliquots are assayed using a Finnigan 4000 GC–MS equipped with a glass column (1.5 m × 2 mm) packed with 3% OV-1 on Supelcoport. Column temperature was 255°C and helium carrier gas flow rate 20 ml/minute. Ion fragments in the protium form at m/e 418 M-[(2 × 90) + 31] and 508[M-(90 + 31)] and the corresponding deuterium ions at m/e 422 and 512 are monitored. Calibration lines of the do/d4 ratio versus do concentration injected were constructed for quantitation.

Table 1 The concentrations of 6-keto $PGF_{1\alpha}$ (picograms/ml) in dog lung perfusates at different times after perfusion began

Perfusion time (minutes)	*DOG* 1	2	3	*Mean ± s.e. mean*
0	100	95	140	112 ± 14
5	250	530	460	413 ± 84
10	360	730	490	527 ± 108
15	390	890	580	620 ± 146
20	410	960	650	673 ± 159
30	490	1150	790	810 ± 191
45	520	1250	890	887 ± 211
60	590	1430	930	983 ± 244