

TDS: Is it a bird, is it a plane ... ? Commentary on Antelman *et al.*, 'Time dependent sensitization (TDS) – possible implications for clinical psychopharmacology'

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During continuous or intermittent treatment with a drug, responses produced by the first administration may either increase or decrease. These are not uncommonly observed phenomena which are referred to by the terms 'sensitization' and 'tolerance'. Although it is generally considered that the continuous impregnation of drug receptors is likely to produce conditions favouring the induction of the compensatory processes which presumably underlie tolerance, there is only limited evidence to support this belief. Much research has shown that the relationships between dosage and intermittency and the timing of drug administration may be complex. This has led to the development of concepts such as behavioural tolerance or sensitization to refer to the ways in which environmental conditions may influence responses to repeated drug treatment (for review see Stewart and Badiani, 1993).

The paper by Antelman *et al.* (1997) deals with a phenomenon which they term 'time-dependent sensitization' (TDS), however they clearly do not wish TDS to be confused with the phenomena studied by pharmacologists under the name of 'sensitization'. TDS is variously described in their review as a 'property', a 'process', a 'hypothesis' and a 'revolutionary concept'. It is said to relate to an organism's responses to the 'foreignness' of a drug, but these responses, it is proposed, are not mediated by the mechanisms involved in the pharmacological effects of the drugs (what kind of mechanisms are involved is not made explicit). TDS is the process whereby '... the responses (to a drug) in that system will grow with the passage of time, up to at least a period of months'. As the authors note, this process, if applicable to the effects of psychotropic drugs used in the clinic, would suggest that current clinical practice, where drugs are given frequently to maintain a constant level of

receptor occupation, is unnecessary. Indeed, this form of drug therapy would actually be counterproductive, according to Antelman *et al.* (1997), because it would tend to give rise to tolerance rather than sensitization (although no explanation is provided as to why this would be the case).

This paper reviews the small number of clinical studies whose results are said to be explicable in terms of TDS. These studies used several designs: loading doses of antidepressants followed by clinical assessment when drugs are no longer present (clearly not a procedure which addresses drug sensitization in the normal sense as drug is not present during the test, but it is apparently relevant to TDS), loading doses followed by a period without drug and then standard daily treatment, and simple intermittent treatment. Some of these trials and experiments produced unusual and not readily explicable results, which might merit further study. Taken together, however, they do not seem to add up to an impressive body of data justifying a complete change of clinical practice. All studies involved small numbers of patients or volunteers, most were not designed explicitly to investigate TDS and few used placebo controls. One study which is presented by the investigators themselves in the context of Antelman's previous work (Deuschle *et al.*, 1997) found that conventional escalating doses of doxepin were more efficacious than pulse dosing, providing no evidence for TDS. Another reference given by Antelman and colleagues as providing 'expanded data' on a recent study with clomipramine (Dube *et al.*, 1996) is in fact an abstract.

An intriguing group of experiments on the effects of triazolam on psychomotor skills in volunteers reported that when the drug was given at weekly intervals the sedative effect appeared to increase. This was an unexpected finding as it is usually considered that

the sedative effects of benzodiazepines show tolerance or remain constant with repeated dosing. Indeed, the same research group had previously found tolerance to the effects of alprazolam tested under similar conditions (Smith and Kroboth, 1987). Although the authors of the papers describing sensitization to triazolam refer to TDS (Kroboth *et al.*, 1995), they themselves note that these observations were 'incidental to the original objectives of the studies'. As no manipulations of relevant parameters such as dosing frequency were attempted, the results remain largely unexplored and unexplained.

The efficacy of many psychotropic drugs in the clinic (perhaps particularly antidepressants) is limited. New and more effective methods of administering such medications would therefore be welcomed. The authors of this paper are to be applauded for drawing attention to this, and proposing a novel approach to drug therapy. The need for a completely new concept of drug action based on undefined (i.e. magical rather than scientific) mechanisms, however, seems doubtful. Certainly, if the authors believe that they have identified a revolutionary form of pharmacology they should try to define exactly how a particular drug should be used in the clinic (i.e. the exact frequency of dosing, high versus low doses, subjects assessed

in the drugged or undrugged state etc.), and carry out a properly controlled clinical trial to test their hypothesis.

REFERENCES

- Antelman, Soares and Gershon (1997) Time dependent sensitization (TDS) – possible implications for clinical psychopharmacology. *Behavioural Pharmacology*, **8**, 505–514.
- Deuschle M, Schmider J, Weber B, Standhardt H, Korner A, Lammers CH, Schweiger U, Hartmann A and Heuser I (1997) Pulse-dosing and conventional application of doxepin: effects on psychopathology and hypothalamus-pituitary-adrenal (HPA) system. *Journal of Clinical Psychopharmacology*, **17**, 156–160.
- Dube S, Perel JM, Miewald J and Kupfer DJ (1996) Antidepressant response to oral pulse loading with clomipramine. *Biological Psychiatry*, **39**, 623.
- Kroboth PD, McAuley JW and Derry CL (1995) Time-dependent sensitization to triazolam? An observation in three studies. *Journal of Clinical Psychopharmacology*, **15**, 192–196.
- Smith RB and Kroboth PD (1987) Influence of dosing regimen on alprazolam and metabolite serum concentrations and tolerance to sedative and psychomotor effects. *Psychopharmacology*, **93**, 105–112.
- Stewart J and Badiani A (1993) Tolerance and sensitization to the behavioral effects of drugs. *Behavioural Pharmacology*, **4**, 289–312.