Parenteral pharmacological treatment of depression:...

PHARMACOKINETIC AND PHARMACODYNAMIC RATIONALE FOR PARENTERAL ADMINISTRATION OF ANTIDEPRESSANTS

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The major concern of administering a drug parenterally instead of orally is that the first passage of the drug through the intestine mucosa, the portal vein and the liver is avoided. For many antidepressants, a substantial fraction of an oral dose will be metabolised during this first pass. The metabolism may lead to elimination of active compounds (e.g., hydroxylation and glucuronidation) or to formation of active metabolites (e.g., through deethylation). As shown for imipramine, the hydrolysis process is saturated during the first pass causing a shift towards deethylation (formation of desipramine). Parenteral administration of imipramine thus, compared with oral administration, results in relatively higher ratio of imipramine vs desipramine in blood. This may have qualitative pharmacodynamic consequences if the parent compound and the desmethyl metabolite have different effects. For imipramine and clomipramine, the parent compound has a strong serotoninergic effect whereas the desmethyl metabolite is largely adrenergic. Parenteral administration of these compounds thus will result in a relatively strongly serotonergic effect. For venlafaxine (V) with 4 active compounds (R and S V and R and S O desmethyl V) all with dual serotoninergic/adrenergic effects, the picture is even more complex. The relative importance of serotonergic and adrenergic effects for the antidepressant response is currently debated, and the possible advantages of using parenteral administration ought to be rigorously tested in randomised trials.

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Intravenous treatment of depressive patients with antidepressants

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Intravenous application of antidepressant drugs is a well established procedure, especially for so-called therapy-resistant patients (Kiehlhoi et al. 1982). As advantages of infusion therapy the following factors have been reported: a more rapid onset of action, an increased therapeutic effect due to higher plasma levels (avoiding first-pass effects and incomplete absorption), fewer side effects by using lower doses, assured compliance and psychological factors. Remarkably few controlled, double-blind studies comparing dip infusion therapy with oral antidepressant treatment have been published; however (Laux et al. 1997). A review of the studies available and the data base of efficacy and tolerability. The WHO collaborative study (Gastpar et al. 1996, Kisholas et al. 1990) and a double-blind study comparing desipramine (IV vs. oral administration) and venlafaxine (IV and PO: 66.7% vs. PO-PO: 63.3%). There were no obvious differences in terms of plasma levels (Laux et al. 1999) are referred as the extensive studies available in this topic.

References:

The psychological and potential psychotherapeutic effects of a slow drop infusion procedure in the initial phase of pharmacological treatment of severely depressed patients still needs to be the subject of systematic and controlled investigations (1). Citalopram (CIT), a SSRI (2), is available.

A multicentre, double blind, double dummy, parallel group, fixed dose study was carried out in two groups of 30 depressive patients to compare efficacy and tolerance of CIT. The drug was given either intravenously (placebo orally) or orally (placebo intravenously) for 10 days (40 mg/day) and then orally till day 42. CIT was measured in plasma (days 10, 21, 42) of the CYP2D6/CYP2C19 phenotyped patients.

On day 11, 33.3% of those patients receiving infusion had a >50% reduction in their baseline HDRS-17 score compared to 17.9% of patients receiving oral medication. At the end of the trial (day 42), there were similar levels of responders (IV-PO: 66.7%, PO-PO: 63.3%). There were no obvious differences with regard to the side effects profile of CIT, between the groups.

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