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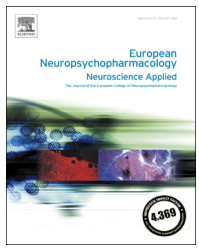

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REVIEW

Tranylcypromine in mind (Part I): Review of pharmacology

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Abstract
It has been over 50 years since a review has focused exclusively on the monoamine oxidase (MAO) inhibitor tranylcypromine (TCP). A new review has therefore been conducted for TCP in two parts which are written to be read preferably in close conjunction: Part I – pharmacodynamics, pharmacokinetics, drug interactions, toxicology; and Part II – clinical studies with meta-analysis of controlled studies in depression, practice of TCP treatment, place in therapy. Pharmacological data of this review part I characterize TCP as an irreversible and nonselective MAO-A/B inhibitor at low therapeutic doses of 20 mg/day with supplementary norepinephrine reuptake inhibition at higher doses of 40–60 mg/day. Serotonin, norepinephrine, dopamine, and trace amines, such as the "endogenous amphetamine" phenylethylamine, are increased in brain, which leads to changes in neuroplasticity by e.g. increased neurotrophic growth factors and translates to reduced stress-induced hypersecretion of corticotropin releasing factor (CRF) and positive testing in animal studies of depression. TCP has a pharmacokinetic half-life ($t_{1/2}$) of only 2 h which is considerably lower than for most other antidepressant drugs. However, a very long pharmacodynamic half-life of about one week is found because of the irreversible MAO inhibition. New studies show that, except for cytochrome P450 (CYP) 2A6, no other drug metabolizing CYP-enzymes are inhibited by TCP at therapeutic doses which defines a low potential of pharmacokinetic interactions in the direction from TCP to other drugs. Insufficient information is available, however, for plasma concentrations of TCP influenced by comedication. More quantitative data are also needed for TCP metabolites such as p-hydroxytranylcypromine and N-acetyltranylcypromine. Pharmacodynamic drug interactions comprise for instance severe serotonin toxicity (SST) with serotonergic drugs and hypertensive crisis with indirect sympathomimetics. Because of the risk of severe food interaction, TCP treatment remains beset with the need for a mandatory tyramine-restricted diet. Toxicity in overdose is similar to amitriptyline and imipramine according to the distance of therapeutic to toxic doses. In conclusion, TCP is characterized by an exceptional pharmacology which is different

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to most other antidepressant drugs, and a more special evaluation of clinical efficacy and safety may therefore be needed.

1. Introduction

The pharmacology of the antidepressant drug tranylcypromine (trans-2-phenylcyclopropylamine, TCP) makes it an exceptional member among not only all antidepressants, but also among the pharmacological group of monoamine oxidase (MAO) inhibitors. Nevertheless, only three elementary groups (benzene ring, cyclopropane ring, and an amino group) are combined in a rather unpretentious molecule (Figure 1). TCP was first synthesized in the 1940s as an amphetamine analogue (Burger and Yost, 1948), but was not further investigated for the next 10 years due to low amphetamine-like activity. Retesting it as a MAO inhibitor revealed high activity against this new target (Maas and Nimmo, 1959) and led to more studies in animals (Tedeschi et al., 1959) and humans. TCP was therefore one of the earliest representatives of modern psychopharmacology. The first clinical study using TCP was published also in 1959 and reported results from 52 female patients with "affective depression of various types" who received 30–40 mg/day TCP (21 recovered, 15 much improved) (Petersen and McBrayer, 1959). A hopeful and successful introduction to antidepressant therapy in 1962 was followed by a crash because of a, now, well-known interaction with tyramine rich food. As a result, a mandatory tyramine-reduced diet was implemented in patients treated with TCP after initially being withdrawn in the USA for some months in 1964. Clinical applications of TCP never again reached high levels and it steadily declined as additional antidepressants were introduced after the 1980s. Today, in contrast to other antidepressant MAO inhibitors, TCP is available in both the USA and Europe. However, it is also the sole irreversible MAO inhibitor marketed in many European countries, and in others no such drug is currently available. Despite this rather unusual history and distribution, TCP is still investigated in non-clinical and clinical studies of depression. Moreover, TCP has served as a scaffold for new TCP-derivatives, and a lysine-specific demethylase 1 (LSD1) inhibitor activity has attracted strong interest recently outside the area of central nervous system (CNS) disorders (Binda et al., 2010). It may be concluded that TCP is still in the minds of scientists and therapists leading to considerable progress in the future. Nevertheless, no special reviews have been published on TCP since 1965 (Atkinson and Ditman, 1965) despite several reviews on MAO inhibitors used in the treatment of psychiatric disorders in general (Cole and Bodkin, 2002; Fiedorowicz and Swartz, 2004; Gillman, 2011; Krishnan, 2007; Laux et al., 1995; Schwartz, 2013; Shulman et al., 2013; Thase et al., 1995). We undertook a review of preclinical and clinical data of TCP with focus to modern literature including some interesting historic perspectives. This part I summarizes the underlying pharmacology, i.e. pharmacodynamics, pharmacokinetics, drug and food interactions, and toxicology of TCP. The results of clinical research and published clinical experience are reviewed in Part II, which also comprises a meta-analysis of controlled studies of TCP in depression.

2. Experimental procedures

A search in PubMed with the term tranylcypromine and additional terms reflecting the selected key concepts has been conducted. The terms monoamine oxidase, phenelzine and moclobemide have been used instead of tranylcypromine for concepts concerning general research questions on MAO or for concepts including comparison of TCP with other MAO inhibitors. After this screening, likely relevant publications have been selected according to titles and abstracts. A conservative approach was applied for the finding and purchase of relevant original articles if the abstracts left some doubt on the content. This electronic search was completed by hand search for additional eligible publications in important reviews and research articles of a key concept. Because of the great amount of publications (>2000 hits for TCP and >20.000 hits for monoamine oxidase in PubMed) and limits in space, the number of concepts for this review has been restricted to questions of most interest with respect to the clinical application of TCP (review Part II). Thus, the objectives of this review Part I were limited to the most accepted primary and secondary mechanisms of action translating to therapeutic activity, adverse effects and drug interactions as well as important new areas of research. Many areas of the pharmacology of TCP have been excluded which are rarely or less often encountered in the discussion of the psychopharmacological application of TCP. This applies for example to TCP studies of imidazoline binding sites, preclinical studies of activity in different organ systems, preclinical studies of general psychotropic properties, seizure models, interactions with non-CNS drugs, and the questions surrounding TCP in pregnancy. As usual for drugs marketed for a long time, preclinical data are discussed also in the perspective of clinical information and some overlapping may occur therefore in the two parts of the review concerning a key concept, however, without redundancy in the data. Publications in peer reviewed journals were regarded as valid. However, methodically incorrect studies in the perspective of technical development have been rejected. The focus was to studies after 1990. Studies conducted before 1990 have also been used if there was no other work on an objective after 1990 or if older studies provided substantial completion. An almost comprehensive presentation of published TCP data was tried in the paragraph pharmacodynamic drug interactions. A balanced evaluation and citation was used in case of controversial data and discussion in literature.

3. Pharmacology of tranylcypromine

3.1. Neurobiochemistry

3.1.1. Monoamine oxidase (MAO)

MAO (Enzyme Commission [EC] number 1.4.3.4, main group: 1. oxidoreductases) catalyzes the enzymatic oxidation of monoamines according to Eq. (1), i.e. the amine is oxidized

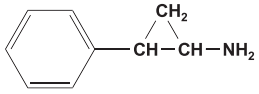

Figure 1 Chemical formula of tranylcypromine (trans-2-phenyl cyclopropylamine).