Pitfalls in Measuring Antidepressant Drugs

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Summary
Depressions being a major problem, antidepressants are one of the most frequently used drugs in the clinical practice. Antidepressants are commonly measured in the laboratory for the purpose of therapeutic drug monitoring. Widely used antidepressants include tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Owing to narrow therapeutic range and higher toxicity, TCAs are a common cause of morbidity and mortality. In emergency situations, the assays of TCAs on urgent basis are needed. Although a number of assays are available for TCA, immunoassays are suitable for screening purpose in case of a suspected overdose. However, immunoassays for TCA also suffer from many limitations including cross-reactivity of active metabolites and are not suitable for therapeutic drug monitoring. Limitations of various assays for estimation of antidepressants and some tips to deal with these limitations are described.

Key Words: Tricyclic antidepressants; SSRIs; immunoassays; interference.

1. INTRODUCTION
Depression affects approximately 10% of men and 20% of women during their lifetime and 3% of the population at any given time (1). It is estimated that 10–15% of the prescriptions written in the USA are for major depression. The patients with depression are at higher risk of suicide and development of cardiovascular disease and myocardial infarction. The World Health Organization predicts that by 2020 depression will be the second (first being heart disease) leading cause of premature death or disability in adults. Therefore, financial and socioeconomic consequences of
depression are very high, and need for antidepressants have been at an all time high. A large number of antidepressants including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and atypical agents are available for treatment of depression (2,3). Although therapeutic ranges for some of these antidepressants is not very well established, need for therapeutic drug monitoring for most of them has been well documented. The antidepressants for which therapeutic drug monitoring is well documented are discussed below in section 2.

2. TRICYCLIC ANTIDEPRESSANTS

TCAs, including amitriptyline, doxepin, nortriptyline, imipramine, desipramine, protriptyline, trimipramine, and clomipramine, were introduced in the 1950s and 1960s. As the name indicates, TCAs have three-ring structure. Although the exact mechanism of their action is not well understood, they are known to inhibit reuptake of norepinephrine and/or serotonin resulting in increased concentration of these neurotransmitters in the synapse. Despite rapid affect on neurotransmitters uptake, their clinical effect may not be seen for weeks after initiation of therapy, indicating that the mechanism of action of TCAs is more complicated than simply increasing the concentrations of neurotransmitters. This is further substantiated by the fact that not all the compounds that inhibit neurotransmitter uptake are antidepressants (e.g., cocaine and amphetamines). In addition to their use as antidepressants, TCAs are used in the treatment of obsessive-compulsive disorder, attention-deficit hyperactivity disorder, school phobia, and separation anxiety in the pediatric population. In adults, they are also used in treatment of neuralgic pain, chronic pain, and migraine prophylaxis, amongst many others (2,4).

Although effective in the treatment of a number of disorders, TCAs are associated with high morbidity and mortality because of their side effects (5,6). These side effects include hypotension, dizziness, and sedation by blocking \( \alpha_1 \) adrenoreceptors; weight gain and sedation through \( H_1 \) histamine receptors; and dry mouth, blurred vision, constipation, and urinary retention through \( M_1 \) muscarinic receptors. TCAs are known to lower thresholds for seizures. TCAs were the third leading cause of toxic exposures in 2004 after analgesics and sedatives (7).

2.1. Pharmacokinetics and Metabolism of TCAs

Most of TCAs are well absorbed and reach peak plasma concentrations within 2–12 h. Owing to their lipophilic properties, they have a very large volume of distribution. Many of TCAs are tertiary amines and are metabolized by the cytochrome P450 isoenzyme system to secondary amines, which are also active. Some TCAs are metabolized to hydroxylated metabolites that may also be active and are further metabolized by glucuronidation. Some pharmacokinetics properties of TCAs are summarized in Table 1. When interpreting data, it is important to keep in mind that these values, at best, are approximate, and there is a considerable inter-individual variability. Some of the factors responsible for these variations are discussed below in section 2.2.