**Ethical, legal and social issues in toxicology**

**Editors Message: Scientific committee**

Toxicology as a science can only thrive when we seek to appreciate ethical, legal and social issues in toxicology and then we wouldn’t be stumbled by the complications of such issues when we become decision makers.

Pioneers in science have comprehended this major issue, and considered it as a fundamental in toxicology as we put in practice, they understood the effect of these terms in research, decision-making and the life itself. And since we believe and according to Aristotle that “Educating the mind without educating the heart is no education at all” we cite the principles of ethics in science. These principles can be a subject for public debate and can deviate according to societies traditions, religious or humanitarian experiences, but in general they can be summarized as follows:

- **Dignity**: which includes the respect of human and animal subject's autonomy.
- **Veracity**: the adherence to transparency and presentation of all the facts, so all parties can discover the truth.
- **Justice**: This includes an equitable distribution of the costs, hazards and gains.
- **Integrity**: an honest and forthright approval.
- **Responsibility**: the acknowledgment of accountability to all parties involved and finally sustainability: which means consideration of actions can be maintained over a long period of time (gilbert and eaton 2009).

Within this contrast in concepts, the only fact that should be heard in our minds is that preservation of lives, environment and justice should be constrained by ethics and the social issues that govern our profession as toxicologist.

Toxicologist, though, should not set back and watch, shouldn’t refrain from absorbing or understanding such principles. Quite The contrary we should use and share the knowledge we gain within the boundaries of ethics, legal and social aspects of our life. After all, actions indeed are the sole reflection of our ethics and virtues.

Reference:

**ISSUE THEME: Benzhexol**

1.1 what is Benzhexol

Trihexyphenidyl (THP) or Benzhexol (trade name Artane) exerts a direct inhibitory effect upon the parasympathetic nervous system, with a relaxing effect on smooth musculature, both exerted directly upon muscle tissue itself. This compound has central nervous system (CNS) depressant effects when taken in small doses and CNS stimulatory effects in large doses. Tolerance, however, to the effects of Benzhexol can occur with prolonged use.

It prevents the effects of acetylcholine, by blocking its binding to muscarinic cholineric receptors at neuro-effector sites on smooth muscle, cardiac muscle and gland cells in peripheral ganglia and in the CNS (1).

This drug is frequently used in the treatment of Parkinson disease and to counteract the extrapyramidal side effects of certain antipsychotic drugs (2).

Benzhexol is well absorbed from the gastrointestinal tract (GIT) and exerts its action within 1 hour of oral dose, and 60% of the dose is excreted in the urine. Hydroxyl THP is the major metabolite present in plasma and urine and accounts for the 2/3 of the THP present in Urine (3).

Mostly Ethanol and CNS depressants such as anxiolytics, sedatives and hypnotics prominently can boost the sedative effect of Benzhexol. Forensic importance is crucial, due to the current incremental abuse and overdose. Nevertheless, fatal poisoning is infrequent (1). Side effects are common and include dry mouth, gastrointestinal disturbances, dizziness and blurred vision. Less commonly, psychotic disturbances have been reported with therapeutic doses.

With all stated toxic doses, psychosis have occurred and manifested by the emotional liability, confusion, suspicion, and hallucination, disorientation in time and place and notably fluctuating consciousness. (2).

Benzhexol overdose produces distinctive central symptoms of atropine intoxication (the central anticholinergic syndrome). Proper diagnosis depends upon recognition of the Peripheral signs of parasympathetic blockade: including fever. Collectively, cardiovascular effects of overdose are tachycardia and hypertension, though, with increasing doses cutaneous vasodilation and hypotension may occur. Other reported effects include lip smacking and tasting movements. The condition can proceed to stupor, coma, paralysis, cardiac and respiratory arrest and, eventually, death.

References:
The Jordanian experience

1.2 Benzehxol Studies in the kingdom

Benzhexol abuse was noticed with increased frequency among Jordanian youth in a study early 1996, and in this study which involved most abused drugs, benzhexol was the second most abused and seized drug from 1996 – 1999, by 29%, following heroin 38% (table 1). Therefore, it was necessary to find proper methods to diagnose benzhexol abuse and better approaches to analyze this drug of abuse in biological samples (1).

Table 1: Number of seized cases, which were analyzed in police forensic science laboratory security directorate from 1996 -1999

<table>
<thead>
<tr>
<th>Year</th>
<th>Heroin</th>
<th>Cannabis</th>
<th>Artane</th>
<th>Amphetamine</th>
<th>Procyclidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>55</td>
<td>18</td>
<td>35</td>
<td>15</td>
<td>10</td>
<td>133</td>
</tr>
<tr>
<td>1997</td>
<td>49</td>
<td>15</td>
<td>44</td>
<td>18</td>
<td>5</td>
<td>131</td>
</tr>
<tr>
<td>1998</td>
<td>65</td>
<td>20</td>
<td>50</td>
<td>20</td>
<td>15</td>
<td>170</td>
</tr>
<tr>
<td>1999</td>
<td>41</td>
<td>22</td>
<td>30</td>
<td>17</td>
<td>5</td>
<td>115</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>75</td>
<td>189</td>
<td>70</td>
<td>35</td>
<td>549</td>
</tr>
</tbody>
</table>

Hadidi has developed a sensitive method for the determination of the commonly abused anticholinergic drugs in Jordan and these trihexyphenidyl, procyclidine, biperiden in plasma and urine using solid phase extraction (SPE) and gas chromatography- mass spectrometry (GC- MS). This method has been applied to forensic and authentic samples taken from abuser and patients using these drugs (2).

Al. Nsour and Hadidi (2002) have introduced the analysis of hair for the misuse of drugs, where it helps in the collection of long term use and determination of compliance with treatment programs.

Benzhexol was found in complete hair in all cases, thus analysis of complete hair would be as good as the use of hair roots and tips. Hair can be used as an alternative to blood and urine in investigating benzhexol abuse. Especially in cases where patients have stopped taking the drug few days before being reported to the forensic clinic and according to the authors, segmental analysis of hair is recommended (3).

In conclusion: Forensic toxicologists usually confront controversial issues in drug abuse cases and these include personal history of drug use which mostly lacks accuracy, or is under-reported or denied, when fearing of legal consequences and embarrassment from admitting illicit substance use is the key feature with most users. Oftentimes, Benzhexol abusers preferred to admit the intake of kemadrin, akineton due to the less severe legal consequences with the two aforementioned drugs.

In contrast, in the differential diagnosis of the three drugs, clinical judgment is the only measure for abuse and unfortunately, the three drugs share the same clinical effects on the abuser, making the clinical judgment complex and unjust.

Therefore, novelty of the developed methods set forth a valuable approach to law enforcement and legal medicine services in the diagnosis of anticholinergic drugs.

References:

Case study

1.3 fatal death

A 59-year-old woman found dead in the house where she lived alone. She had a history of paranoid disorder and suffered from persistent delusional disorder (IDC-F22) and has been being treated. Neither suspicious circumstances for her death, nor a suicidal note were found at the scene. Her medication regimen was frequently changing, and each change was accompanied by her complaint of palpitations. The latest therapy approach included: fluphenazine 25 mg injection, received 3 weeks before fatality; and Artane (THP hydrochloride 15 mg / day). They last saw her 3 days prior to death.

Autopsy Report: The woman was 152 cm tall and weighed 55 kg.

External examination: yielded no evidence of external injuries or violence.

Autopsy findings: revealed no marked pathological changes.

Histological: only vacular degeneration and cholestasis in liver.

Sampling: Femoral venous blood, urine, bile, and gastric contents were collected for toxicological analyses.

Toxicology Report: To reveal the presence of different drugs and / or metabolites in biological materials, samples were extracted separately from acidic (pH 2; 2M H2SO4 is added) and alkaline (pH 9; K2CO3: NaHCO3 = 2.3 and 25% NH4OH are added) media. GC-MS analyses were performed after confirmation of the presence of acidic and / or basic drugs (by matching both the retention time and full scan spectra of an unknown peak with a standard). In this case, the presence of THP and hydroxy-THP has been detected by screening method and the quantitative analysis was carried out by extraction method from alkaline media. Ethanol was analyzed in femoral venous blood and urine by headspace GC with a flame ionization detector (headspace GC-FID). Results from toxicological analyses are given in Table 1.

Table 1: Tritexyphenidyl and ethanol concentration in tissues of the victim

<table>
<thead>
<tr>
<th>Detected</th>
<th>Femoral venous blood</th>
<th>Urine</th>
<th>Bile</th>
</tr>
</thead>
<tbody>
<tr>
<td>THP</td>
<td>0.053 mg/L</td>
<td>0.56 mg/L</td>
<td>ND</td>
</tr>
<tr>
<td>Hydroxy-THP</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.096 g/L</td>
<td>0.100 g/L</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table: Detected substances in tissues of the victim

Qualitative GC-MS analysis confirmed the presence of THP in blood and urine, and hydroxy-THP in blood, urine, and bile. The presence of these substances and other xenobiotics was not confirmed in gastric contents.

Interpretation: THP concentrations were found to be 0.053 mg/L in femoral venous blood, and 0.560 mg/L in urine. The blood and urinary ethanol concentrations were 0.096 and 0.100 g / L, respectively. Based on these results, investigators determined the cause of death to be THP poisoning. It is suggested that rare case of death associated with THP overdose should be taken in conjunction with central nervous system depressants (benzodiazepines, ethanol) and / or with other pathological disorders. However, according to the author, the case could not be supportive for this assertion. The circumstances of the case excluded homicide. On the other hand, data were not sufficient to determine neither suicide nor accident as a cause of death (1).

References:
From What I read and Liked

1.1 Tolerance, dependence and sensitization

Psycho-stimulants have both acute and permanent effects on behavior. They acutely increase alertness and produce a sense of well-being, like some of drugs of abuse such as cocaine and amphetamine, which are used repeatedly and quite frequently (1).

Therefore, some acute drug effects may diminish (tolerance) while others are enhanced (sensitization). Neural mechanisms of tolerance can mask the expression of sensitization, but may fade more rapidly.

A drug abuser who abruptly stops active drug use may display withdrawal symptoms. Some drugs give rise to clear physical symptoms of withdrawal such as hypertension or abdominal cramps after stopping opiates use, or seizures after stopping alcohol use. All addictive drugs, including psycho-stimulants can produce emotional withdrawal symptoms such as dysphoria, anhedonia (an inability to experience pleasurable emotions from normally pleasurable life events), and diminished capacity of experiencing pleasure. Moreover, tolerance and withdrawal are the defining aspects of drug dependence. In contrast, human addiction is defined by uncontrolled compulsive drug use despite negative consequences.

Dependence is strictly defined and can occur without addiction (e.g., in patients requiring morphine for cancer pain or benzodiazepines for panic disorder). In addition to being insufficient for addiction, dependence is also not necessary. Both withdrawal symptoms and drug tolerance tend to disappear within a few days or weeks and consequently, unlikely to account for the persistence of drug addiction. Therefore, it is important to distinguish between neural alterations that account for dependence and thus responsible for compulsive drug use and late relapse (1).

### Hypothetical scheme of the changing Neural substrates for addictive drug use (1)

<table>
<thead>
<tr>
<th>Phase of drug use</th>
<th>Cumulative reasons for drug use</th>
<th>Possible neural systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Experimentation, self medication, peer group behavior</td>
<td>?</td>
</tr>
<tr>
<td>Early medium</td>
<td>PLUS: Explicit memories of pleasure, increased incentive value of drug-related stimuli</td>
<td>Synaptic plasticity in hippocampus, amygdala and their projections to ventral striatum</td>
</tr>
<tr>
<td>Later/relapse</td>
<td>PLUS: Relief of avoidance of withdrawal symptoms</td>
<td>Compensatory adaptations in many brain regions, including striatum (and locus ceruleus for opiates)</td>
</tr>
<tr>
<td></td>
<td>PLUS: Automatized stimulant-response habits</td>
<td>Synaptic plasticity of neocortical projections to dorsal striatum</td>
</tr>
</tbody>
</table>

**Summary**

Use of psycho-stimulants is incredibly increasing and widespread. The majority of psycho-stimulants users will not experience significant adverse effects from their use of these drugs. However, the cumulative number of users, and the use of the more potent crystal form of methamphetamine, to point to an increase in problems associated with psycho-stimulant use (2). Nonetheless, drug addiction describes the motivational strength of substance use; drug abuse describes the misuse of a substance without precise reference to motivational strength; and drug dependence describes the need of using a substance to maintain normal psychological and/or somatic functioning without reference to the motivational strength of the substance use or to whether the substance use violates cultural norms. These three terms have distinctly different meanings although there are obvious and numerous cases where all three apply to the same drug-use situation (i.e., the individual may be dependent upon a drug which they abuse because they are addicted).

**Reference:**