

Producing Chemical Toxicity – Could it be Because of Actually Losing Tolerance?

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Received: September 30, 2016; **Published:** November 07, 2016

It is almost an accepted dogma that tolerance has occurred when a person no longer responds adequately to doses of a medication that were initially effective and higher doses were then required to achieve that initial effect. This loss of response is known to continue, increasing addiction liability, and in some cases producing fatal outcomes. This is a very common occurrence with the use of opioids/opiates for the treatment of moderate to severe pain, leading to the current opioid epidemic worldwide. On the other spectrum are individuals that may respond adversely, sometimes to the same degree of toxicity, to normal doses of a drug that the general population appears to tolerate very well. It is now clear then that our responses to medications, and their efficacy, depend on several factors. Pharmacokinetic principles describe very well the fate of drugs and chemicals during hepatic metabolism, undergoing both phase I and II metabolic processes. The role that various cytochrome P450 (CYP450) enzymes play during phase I reactions have become very important and make up the pillars upon which personalized medicine is being built. Four distinct metabolizers are now recognized (slow, extensive, intermediate and ultra-rapid), known to be genetically determined and can be explained by the CYP450 enzyme polymorphism in different populations of people. During transport of ingested drugs in the peripheral circulation, specific receptors in the various tissue beds bind and extract the drugs against a concentration gradient and upon arrival inside target cells, a host of biochemical events lead to producing specific pharmacological responses, such as analgesia in the case of pain medications. The concept of drug tolerance is rooted in either the changes that an opioid makes to the receptor numbers (down and up-regulation) or the adenylate cyclase enzyme post-receptor binding after repeated dosing. For ultra-rapid metabolizers for which the drug never seems to reach the therapeutic window, it is predictable that therapeutic failure may result and in slow metabolizers in which a large amount of the parent drug does not get metabolized, and the therapeutic range is reached very rapidly and this may lead to toxic reactions. These fit very well in the old paradigm.

We are increasingly being exposed to high levels of environmental toxicants and as chemicals it can be predicted that they would have some effect on the response to drugs/chemicals. This must be considered in the pathogenesis of tolerance. The concept of multiple chemical sensitivity syndrome (MCS) is rapidly growing and although rejected by several medical associations, it is conceivable that some of the most important elements of MCS, for example, that sensitivity can be acquired after prior exposure to an environmental toxicant and transferred to multiple organ systems is appealing. Environmental toxicants include a host of compounds, such as outdoor and indoor air pollutants, food additives, tobacco smoke etc. Because the insulting chemical exposure levels are generally low and no organs per se are damaged, it is often dismissed. It is now well documented that some people who previously tolerated drugs and chemicals have suddenly lost those tolerances upon a change of location/environment (and sometimes without change of environment). Consider the possibility that the loss of tolerance could be toxicant-induced so that a new paradigm would be the development of toxicity because of the loss rather than development of tolerance. As illustrated in Figure 1, it can be imagined that an individual is initially not sensitive, i.e. tolerant to the drug (intact onion) but after a protracted period of exposure to environmental toxicants, akin to peeling the skin off and cutting the onion, the tolerance begins to peel off. One could imagine then the situation where a normal dose of a drug producing toxic reactions. The term Toxicant-induced loss of tolerance (TILT) has been proposed by several investigators. Several factors may hasten the creation of the susceptible individual, such as heredity, the amount of indoor pollutants inhaled, prior exposure to certain drugs or chemicals, perfumes and colognes, foods, caffeine, stress level or even gender. Studies are probably now warranted to examine the effect of these “environmental” factors on drug “sensitivity”, in relation to blood drug levels, and cytochrome enzyme polymorphism.

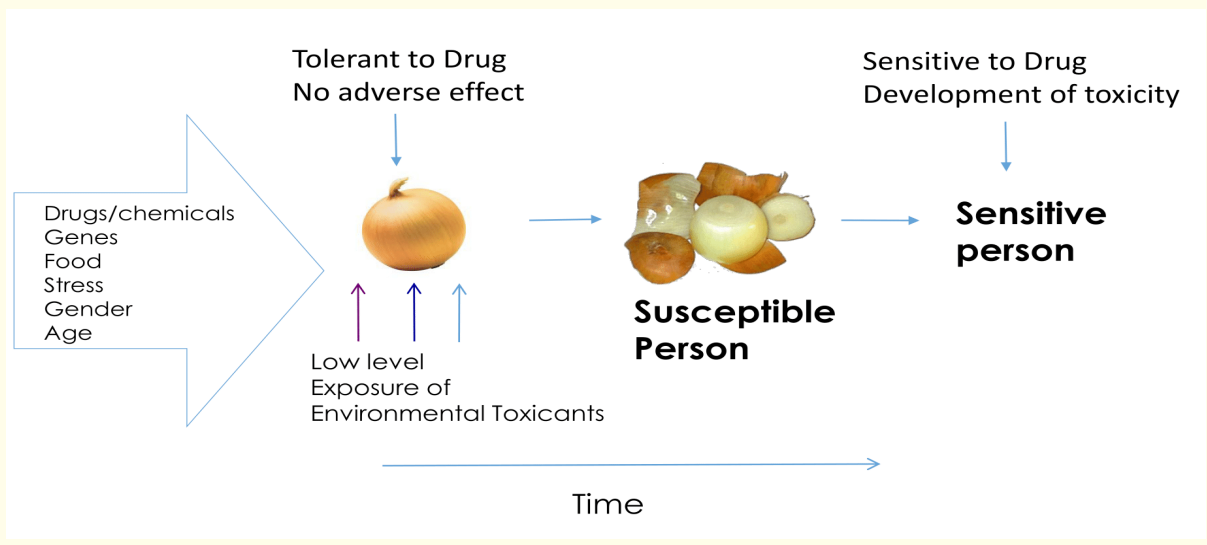


Figure 1: The tolerant individual is exposed to low levels of environmental toxicants, which peels out the tolerance, making the same drug intolerable after a while.

Volume 2 Issue 4 November 2016
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