

Katzung's Basic & Clinical Pharmacology, 16th Edition

Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition



MOTO & VISION



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

UMAR'S MODEL OF INTEGRATION



Learning Objectives

At the end of the academic session, students of 3rd Year MBBS will be able to ;

- Define tolerance & tachyphylaxis with clinical examples
- Differentiate between tolerance and tachyphylaxis
- Discuss different types and mechanism of drug tolerance
- Identify strategies to minimize or prevent the development of tolerance and tachyphylaxis in clinical practice
- Discuss the clinical implications of tolerance and tachyphylaxis

CORE SUBJECT

TOLERANCE

Progressively diminished pharmacological response to drug at a certain dose following repeated or prolonged

exposure, and requiring increasing dosages to achieve the

desired effect on subsequent administrations

DEVELOPMENT OF TOLERANCE





CHARACTERISTICS OF TOLERANCE



- 1. It mainly occurs with drugs acting on CNS. (Opioids, Benzodiazepines, Alcohol)
- 2. Reversible, once exposure to the drug is discontinued or the dose is increased
- 3. As higher dose is required to produce the initial response obtained at a lower dose, so DRC shifts to right.
- 4. Dependent on the dose and frequency of drug exposure
- 5. Variable time course and extent of tolerance development between different drugs.
- 6. Not all drug effects develop the same amount of tolerance.
- 7. Takes days to weeks to develop



CHARACTERISTICS OF TOLERANCE

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TYPES OF TOLERANCE



□ INNATE TOLERANCE (NATURAL TOLERANCE)

Genetic insensitivity to a drug, observed on first administration of drug a) Black races are tolerant to Mydriatics b) Rabbits are tolerant to Atropine

□ ACQUIRED TOLERANCE

After repeated use of a dug in an individual who was initially responsive to it.

TYPES OF ACQUIRED TOLERANCE

- Pharmacokinetic tolerance (dispositional /metabolic)
- Pharmacodynamic tolerance (cellular)
- Learned tolerance
 - Behavioral
 - Conditioned
- Cross tolerance
- Physiological tolerance (pseudotolerance)
- Reverse tolerance/sensitization



Pharmacokinetic Tolerance

- Occurs when repeated use of a drug changes its pharmacokinetic properties & reduces the amount of the drug available at the target site
- Increase in the rate of metabolism of the drug
- Enzyme induction & auto induction (carbamazepine, barbiturates)



Pharmacodynamic Tolerance

- Occurs when repeated use produces adaptive changes within systems so that response to a given concentration of the drug is reduced
- Drug-induced changes in
 receptor density
- efficiency of receptor coupling to signal transduction pathways

Example:

- Receptor uncoupling (Morphine)
- ↓ number of receptors e.g. β2 agonist (Salbutamol)



MECHANISM OF PHARMACODYNAMIC TOLERANCE

Desensitization of receptors

Desensitization is characterized by either a change in coupling of signal transduction pathways to receptors or by internalization of receptors into the cell

• Downregulation of receptors

Downregulation of receptors reduces the number of functional receptors on the cell surface.

SPIRAL INTEGRATION WITH BIOCHEMISTRY

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LEARNED TOLERANCE

Reduction in the effects of a drug due to compensatory mechanisms that are acquired by past experiences

Behavioral tolerance

Conditioned tolerance



LEARNED TOLERANCE

Behavioral tolerance:

- The skills that can be developed through repeated experiences with attempting to function despite a state of mild to moderate intoxication.
- At higher levels of intoxication, behavioral tolerance is overcome, and the behavioral deficits are obvious.
 - e-g Learning to walk a straight line despite the motor impairment produced by alcohol intoxication.

LEARNED TOLERANCE

- **Conditioned tolerance** (situation/context specific tolerance):
- Develops when repeated drug use reduces its effect in the environment where it is typically administered, but not in other environments.
- If a drug always is taken in the presence of specific environmental cues (e.g., smell of drug preparation and sight of syringe), these cues begin to predict the effects of the drug, and the adaptations begin to occur, which will prevent the full manifestation of the drug's effects



When tolerance to one drug diminishes the effect of another drug

- Generally occurs between drugs of the same class
 Opioids: Morphine, Methadone
- Can occur between drugs with similar pharmacological effects
 CNS depressants: Morphine & Barbiturates
- Useful in medical management of drug dependence/detoxification Heroin addict is given methadone.

REVERSE TOLERANCE (SENSITIZATION)



- An increase in response with repetition of the same dose of the drug.
- Sensitization results in a shift to the left of the dose-response
- Sensitization can occur with stimulants

such as cocaine or amphetamine

TACHYPHYLAXIS (ACUTE TOLERANCE)

- It is rapidly developing reduction in response when same doses of some drugs are repeatedly given over short intervals / in quick succession.
- Rapid tolerance developing with repeated use on a single occasion, such as in a "binge." Repeated doses of cocaine over several hours produce a decrease in response to subsequent doses of cocaine during the binge.



TACHYPHYLAXIS (ACUTE TOLERANCE)



Figure 1-16. Effect of repeated doses of adrenaline (upper graph) and ephedrine (lower graph) on blood pressure in anaesthetised dog. Arrows denote administration of the same doses.

Effect of repeated doses of adrenaline is similar. It does not show tachyphylaxis. Exphedrine, an indirectly acting drug, shows tachyphylaxis as effect of repeated doses is progressively decreased.

Tachyphylaxis after repeted ephedrine administration (decrease ineffect on blood pressure)



E = ephedrine administration



TACHYPHYLAXIS (ACUTE TOLERANCE)

Mechanism:

Depletion of stores of mediators

Example: Indirectly acting sympathomimetics

e.g. Tyramine , Amphetamine , Ephedrine.

Tachyphylaxis can be overcome by:

Increasing the interval between doses

VERTICAL INTEGRATION WITH MEDICINE

- Tolerance to drugs used in chronic diseases
- Anti hypertensives (beta blockers)
- Opioid analgesics
- Main characteristic of drugs acting on CNS (drugs of abuse)



 Ilan, Y., 2022. Next-Generation personalized medicine: implementation of variability patterns for overcoming drug resistance in chronic diseases. *Journal of Personalized Medicine*, *12*(8), p.1303.



BIOETHICS

Brett Favre says he used to take a month's worth of painkillers in two days

"I don't remember the dynamics of how it worked, but say two gave me an effect I liked," Favre said. "After a month, two didn't do anything, so you needed three. And it may have been less [time] than that. And then four and then so on and so forth. I don't remember how long it took until you had to graduate to more, but I knew 15 was hard to come by."

ARTIFICIAL INTELLIGENCE

Bouleftour, W., Viard, A., Mery, B. *et al.* Body surface area capping may not improve cytotoxic drugs tolerance. *Sci Rep* 11, 2431 (2021). https://doi.org/10.1038/s41598-021-81792-6



END OF LECTURE ASSESSMENT

1. Rapid decrease in response to a drug only after a few doses is termed as:

- A. Antagonism
- B. Desensitization
- C. Resistance
- D. Tolerance
- E. Tachyphylaxis *

2. Main factor causing tachyphylaxis is;
A. Change in the efficiency of the receptors
B. Decrease in metabolism of drugs
C. Depletion of neurotransmitters *
D. Increase in metabolism of drugs
E. Increase in amount of neurotransmitters

- 3. Tolerance produced by enhanced metabolism of a drug is termed as
- A. Cross tolerance
- B. Inverse tolerance
- C. Pharmacokinetic tolerance*
- D. Pharmacodynamic tolerance
- E. Reverse tolerance
- 4. Tolerance to one drug confers the tolerance to other drug of the same category is called as
- A. Cross tolerance*
- B. Inverse tolerance
- C. Pharmacokinetic tolerance
- D. Pharmacodynamic tolerance
- E. Reverse tolerance
- 5. Prolonged exposure to a directly acting agonist results in:
- A. Downregulation of receptors *
- B. Depletion of neurotransmitters
- C. Resistance of receptors
- D. Sensitization of receptors
- E. Upregulation of receptors

