Alkylating agents

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Alkylating agents/mechanism of action

- Alkylating agents have ability to form highly reactive carbonium ion or immonium ion intermediates.
- These intermediates linked to high electron density sites such as phosphate, hydroxyl, carboxyl , sulfhydryl and amino groups of protein etc.
- Alkylating agents do alkylation (transfer alkyl group) to these high electron density sites on DNA/protein.
- The N-7 and O-6 position of guanine, N1 and N3 of adenine, N3 of cytosine is more susceptible to make covalent bond with cytotoxic agents.

Alkylating agents/mechanism of action

- Oldest class of cancer chemotherapy, first non-hormonal drugs to be used effectively for the treatment of cancer.
- Alkylating agents exert cytotoxic effects while transfer of their alkyl groups to various cellular constituents.
- Alkylation of DNA within the nucleus probably represent the major interactions that lead to cell death. However these drugs react chemically with sulfhydryl, amino, hydroxyl, carboxyl and phosphate groups of other cellular nucleophiles.
- The general mechanism involves intracellular cyclization of alkylating agents to form an ethylene imonium ion that may directly or through the formation of a carbonium ion transfer alkyl group to a cellular constituent.

Mechanism of action……

- Traditionally these agents are divided into two types: those that react directly with cellular constituents and second that form reactive intermediates which then react cellular constituents.

- On the basis of this, alkylating agents are divided into SN1 and SN2.

- SN1= dependent on the concentration of reactive intermediates (e.g nitrogen mustard and nitrosoureas).
- SN2= dependent on concentration of alkylating agents and cellular constituents (e.g Busulphan)

Mechanism of action .....

- Nitrosoureas involves carbamoylation of lysine residues of proteins through formation of isocyanates.
- The interaction can occur on a single strand or on both strands of DNA through cross-linking. It is irreversible
- This result in miscoding through abnormal base pairing and lead to DNA strand brakeage (interfere with transcription and with replication.
- This action occurs in all cells, but alkylating agents have their primary effect on rapidly dividing cells which don’t have time for DNA repair.
- Cancer cells, hematopoitic, reproductive and endothelial cells are among the most affected

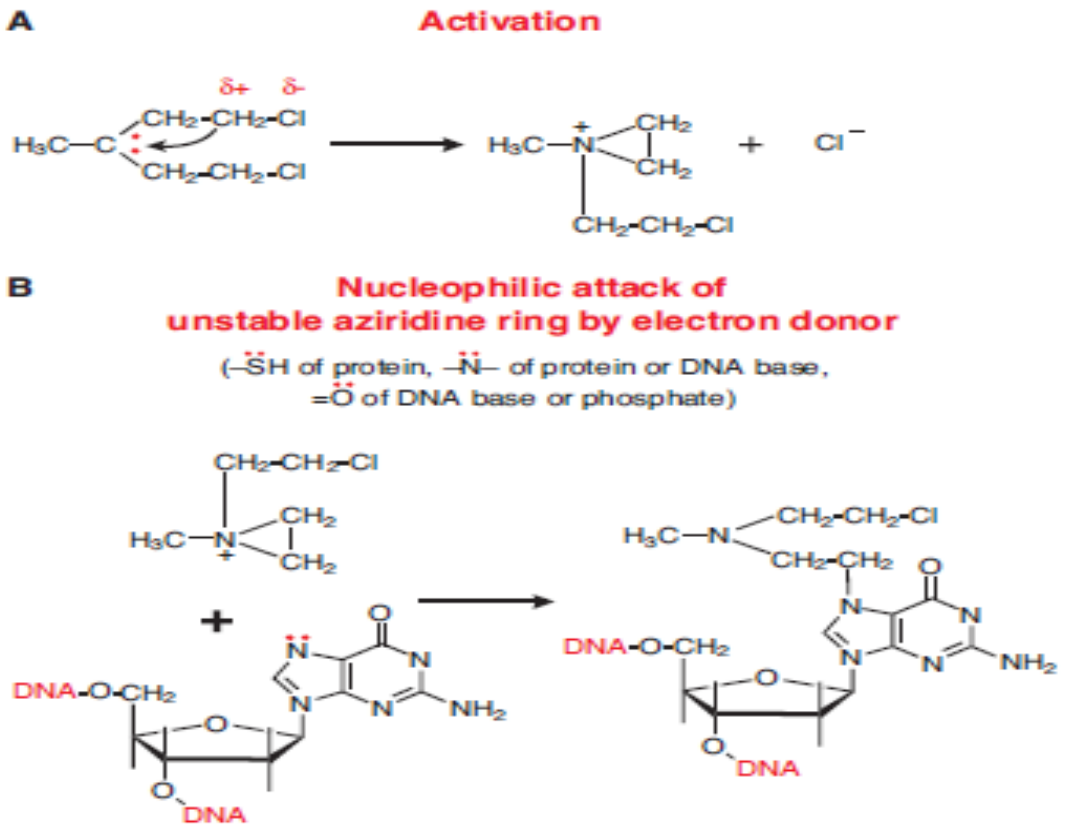

Figure 61–1. *Mechanism of action of alkylating agents.* **A.** Activation reaction. **B.** Alkylation of N7 of guanine.

Adopted from Goodman & Gillman's. The pharmacological basis of therapeutics

Pharmacokinetics

- Alkylating agents can be given through orally, intravenously or subcutaneously.
- The liver microsomal cytochrome P450 enzymes convert alkylating agents into active and inactive metabolites. E.g cyclophosphamide into 4-hydroxy cyclophosphamide (non-polar, enter into cells rapidly) and aldophosphamide. Aldo-phosphamide decompose into phosphoramide which is the first reactive alkylating agent.

Therapeutic indications

- Used for haematologic and solid cancers generally as combination therapy. E.g MOPP
- M=Mechlorethamine
- O=Oncovin
- P=Prednisone
- P=Procarbazine
- Cyclophosphamide as single or in combination used for Burkitt's lymphoma. Hodgkin's lymphoma and breast cancer.
- Nitrosoureas are preferred in brain tumors
- Melphalan (amino acid analogue) is used in multiple myeloma, ovarian cancer and breast cancer

Toxicity and adverse effects

- Toxicities are generally dose related and particularly occur in rapidly growing tissues such as bone marrow, gastrointestinal tract and gonads. Cyclophosphamide produces less GIT and hematopoitic toxicity than other alkylating agent. This is due to that aldehyde dehydrogenase oxidizes aldophosphoramide into carboxyphosphamide, an inactive product that excreted through urine.

Toxicities/adverse effects

- After intravenous injection, nausea and vomiting occur usually 30-60 minutes.
- White blood count and granulocyte count reach their low level 10-12 days after therapy with mechlorethamine and cyclophosphamide.
- Other effect include oral ulcer, cystitis, sepsis, cardiotoxicity