PHARMCOLOGY

SHEET NO. 4

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Sedative-Hypnotic Drugs

- They are drugs which cause sedation (calming effect) with concomitant relief of anxiety or encourage sleep.
- This drug classification is clinical rather than chemical, since these drugs have diverse chemical structure.
- A sedative (anxiolytic) agent should reduce anxiety and exert a calming effect.
- Seductive, anxiolytic effect and hypnosis follow dose-response relationship.

  1)Low dose ➡️sedition

  2)higher dose➡️anxiety will be relieved

  3)higher dose➡️anesthesia

- A hypnotic drug should produce drowsiness and encourage the onset and maintenance of sleep.
- Hypnotic effect involves more pronounced depression of the CNS than sedation, and this can be achieved by increasing the dose.
- Example of dose-response relationships:

- This curve shows Linear relationship; by increasing the dose, We will be transforming from one stage to another
- Coma is a pathological stage/ disadvantage, we want people to be sleep not comatose
- For anesthetic affect we will choose drug A. (We will explain the anesthetic affect in another lecture)
- Drug B is useful for sedation and hypnosis only, (it reaches a plateau, so to reach anesthesia we need very high dose, which is not practical.)

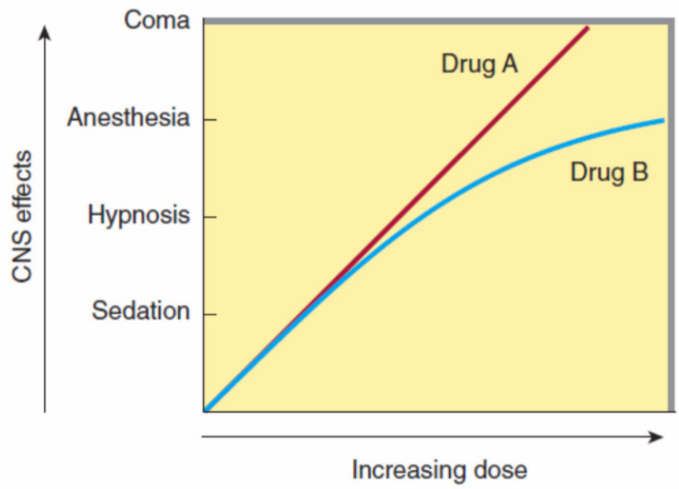


FIGURE 22–1 Dose-response curves for two hypothetical sedative-hypnotics.

Classification

1. Benzodiazepines: Diazepam, Chlordiazepoxide, Flurazepam, Oxazepam, Lorazepam, Nitrazepam, Triazolam, Alprazolam.
2. Barbiturates: Phenobarbital, Pentobarbital, Secobarbital, Thiopental.
   - older than Benzodiazepines, but now They aren't very important because of their long half time ,(not suitable to induce hypnosis). For example secobarbital have 24 hour t½, the patient will sleep for 4 days, Or be dizzy. Phenobarbital has 4 to 5 days of t½ the patient to sleep for 20 days. -Their use is very limited.
   -Thiopental Is used for an intravenous anesthesia to induce sleep
   -Phenobarbital is antiepileptic drug, it makes the patient drowsy so, its use decreased. Now, You can't give an epileptic patient a drug that causes sleep for a long time. It's only used in case of febrile convulsion (High fever convulsion)
3. Chloral hydrate,Used for citation and hypnosis in children
4. New drugs for sleep disorders: Zolpidem, Zaleplon, Eszopiclone.
   - newer than the previous classes (these are known from 20 years).
   -we'll talk about them as zolpidem, But you should know that We mean the whole class.
   -induce sleep only
5. Melatonin receptor agonists (hypnotic): Ramelteon.
   -induces sleep only.
   -melatonin helps in sleeping and is Produced only in the dark by penal gland. penal gland is Calcified early, so the ability to produce melatonin becomes lower.
   -Calcification can occur in young people also, but this is a partial calcification
6. Anxiolytic agents: Buspirone.
   -Doesn't have hypnotic or sedative action

- Balance anesthesia is using multiple drugs at lower doses to decrease the Adverse effects during anesthesia.

Pharmacokinetics

note: Because there's a lot of drugs in this lecture, the Dr will speak about pharmacokinetic and pharmacodynamic in general

- Absorption after oral administration depends on lipid solubility (Can cross the membrane, blood brain barrier and GIT easily). Most of them are well absorbed.
- Passage to CNS also depends on lipid solubility,The more lipid soluble a drug is, the more it enters into CNS (thiopental, triazolam) ➡️ rapid onset of action (but short)

-thiopental → has short duration of action, it Isn't related to the t½ of the drug; it's lipid soluble it enters the CNS from the circulation and induces its action. After a while, the drug will enter the circulation again because its concentration there decreases and the concentration in the brain will decrease so the patient will wake up if you didn't give a second dose, this process is called **Redistribution.**

-triazolam → Has short half-time ➡️ short Duration of action

→ it's lipid soluble ➡️ rapid onset of action

- All of them cross the placental barrier, and if given before delivery, they may depress neonatal vital functions.

-these drugs can't be given Early during pregnancy because of the congenital malformation in fetus (Teratogenic drugs).

-These drugs are the drugs of addiction so, if the mother during pregnancy was addicted to them, the fetus will be addicted too ➡️➡️ so after birth, and because the infant can't take the drug, he/she will have **Withdrawal symptoms**

- Detectable in breast milk and may have depressant effect in the infant.

-Abuser mother can't breastfeed her infant, Because sedative hypnotic cause adverse reaction, tolerance And physical dependence, so if breastfeeding stops, the infant will have symptoms of withdrawal.

-This is why these drugs can't be given during pregnancy or lactation.

- Metabolic transformation is the main (but not the only one) mechanism of elimination of most sedative- hypnotics.

-For example benzodiazepines, Almost all of them are eliminated by metabolism but differ in metabolizing enzymes

- Hepatic metabolism accounts for the clearance of all benzodiazepines.
- Most of them undergo oxidation by cytochrome P450 enzymes (CYP3A4), and subsequently conjugated to glucuronides that are excreted in urine

* CYP 3A4 Exist in the liver and intestines, it's amount Differs among people, it causes
drug-drug interaction because it's responsible for metabolism of 50% Of clinical available drugs that are Eliminated by metabolism.

*Grapefruit kills this in enzyme, It is a suicide substrate ➡️ One cup of grapefruit juice Will erase this enzyme from the liver for at least 24 hours and You can't have new enzyme unless you have a new protein that can synthesise this enzyme.

- Many products of oxidation of benzodiazepines are pharmacologically active, some with longer half-lives than parent drug (desmethyldiazepam has a t½ of > 40 hours).

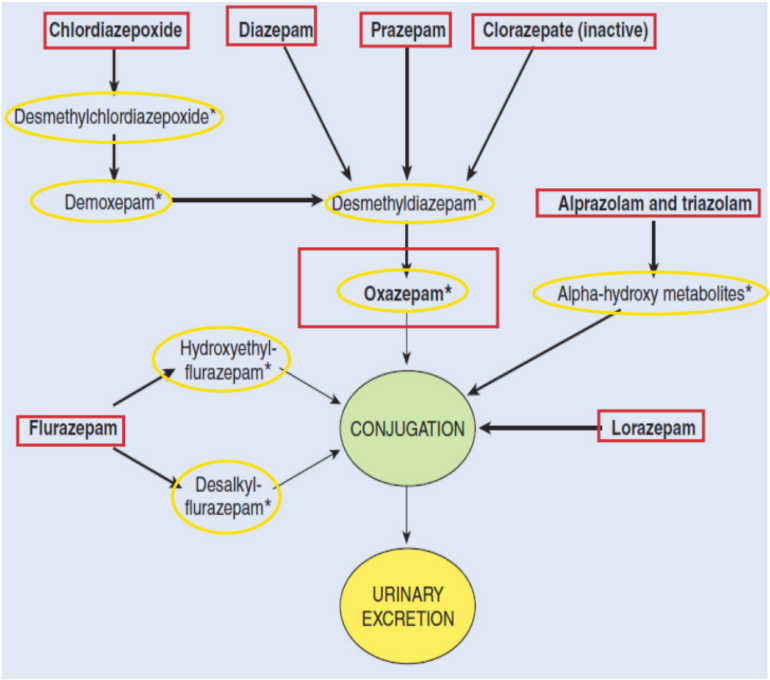
It is active as much as benzodiazepines

- Metabolism is affected by inhibitors and inducers of CYPs.

-when drugs are metabolized by the same enzyme, they will compete With each other on the active site ➡️ this decreases their Metabolism

- 👱‍♀️ ⚕ doctor's advice : When you go to the hospital make sure to know the inducers and inhibitors of the CYPs and check if the patient has any drug-drug interaction.

-**isoenzymes** (eg, P450) Have inducers and inhibitors, Inducers that increase the concentration of the enzyme and increasing the metabolites activity so decrease the Pharmacological action. The inhibitors of the enzyme will decrease the metabolism and increase the duration of the Drug



-Active metabolites result from drugs oxidation.
- Oxazepam: It is an active metabolites and drug by its own, when it is give as a drug it conjugates with Glucuronic acid directly.
-Lorazepam: This drug doesn't go under Oxidation and conjugate Directly
-you can notice that Diazepam, prazepam, clorazepate and demoxepam Will produce desmethyldiazpam.

TABLE 22–1 Pharmacokinetic properties of some benzodiazepines and newer hypnotics in humans.

Drug	Tmax (hours)[1]	$t_{½}$ (hours)[2]	Comments
Alprazolam	1–2	12–15	Rapid oral absorption
Chlordiazepoxide	2–4	15–40	Active metabolites; erratic bioavailability from IM injection
Clorazepate	1–2 (nordiazepam)	50–100	Prodrug; hydrolyzed to active form in stomach
Diazepam	1–2	20–80	Active metabolites; erratic bioavailability from IM injection
Eszopiclone	1	6	Minor active metabolites
Flurazepam	1–2	40–100	Active metabolites with long half-lives
Lorazepam	1–6	10–20	No active metabolites
Oxazepam	2–4	10–20	No active metabolites
Temazepam	2–3	10–40	Slow oral absorption
Triazolam *	1	2–3	Rapid onset; short duration of action
Zaleplon *	< 1	1–2	Metabolized via aldehyde dehydrogenase
Zolpidem *	1–3	1.5–3.5	No active metabolites

[1]Time to peak blood level.

[2]Includes half-lives of major metabolites.

Don't be horrified from the numbers, they were mentioned to show how long their effects last

-Pay attention to t½, because drugs with lower t½ are more suitable to be administrated.
-3 to 4 hours of t½ means sleeping the whole day.
-this table is important to determine the best hypnotic for your patient .

- * Suitable to be used as hypnotics, Because Sedative hypnotic drugs are effective in putting the patient into sleep (Effective in people who have trouble falling asleep, but these drug don't work for whom wake up multiple times during the night,) So you want a drug with short duration to make you fall asleep 8 hours for example, then, wake up for your university and work.
- A drug like diazepam has t½ of 50 hours (as an average), and desmethyldiazepam has 40 hours = 90 hours ➡️ 90*4= 360 hours 360/24 = 15 days➡️ Not suitable for hypnosis/inducing of sleep at all.
- Drugs that Conjugate directly with a glutamate like oxazepam and lorazepam have 15 hour of t½
- Barbiturates are also mainly metabolized by oxidation pathways then conjugated.
- Phenobarbital is 20-30% excreted unchanged in urine, and its excretion is increased by alkalinization of urine

-If you by mistake give the patient high dose of Phenobarbital and patient starts to feel sedation, Drowsiness and sleepy, you can eliminate this effect by preventing the 20 - 30% from getting reabsorbed again from the renal tubule, And Increasing the drug Excretion with urine

-The urine is alkalized By sodium Bicarbonate orally or intravenously

-Phenobarbital is an organic acid that will be in ionized form after it alkalis the urine, and ionized forms don't cross membranes, hence it won't be absorbed in renal tubules, and it will be excreted in urine

urine is alkalized ➡️ Phenobarbital is ionized ➡️ Phenobarbital won't be reabsorbed in renal tubule ➡️ increase elimination of drug with urine

- The rate of metabolism is usually slow, with long elimination half-lives:

  Secobarbital and pentobarbital ~ 18 - 48 hours.
  Phenobarbital ~ 4 - 5 days.

- Multiple dosing with these agents can lead to cumulative effects (as long half-life BDZ),they will accumulate in the body.
- Zolpidem, Zaleplon, and Eszopiclone are metabolized to inactive metabolites by CYP3A4.
- Cimetidine and Ketoconazole inhibit their metabolism, while rifampin induces it.

GABA

- It is an inhibitory neurotransmitters, typically released from local interneurons.
- Interneurons that release GABA are present throughout the CNS, including the spinal cord And brain.
- GABA receptors are divided into 2 main types: GABAA and GABAB
- IPSPs (inhibitory postsynaptic potentials) in the brain have a fast and a slow component. The fast component is mediated by GABAA receptors and the slow component by GABAB receptors.
- **GABAA** receptors are ionotropic receptors and are selectively permeable to Cl-

-When the chloride enters the cell it becomes More negative or hyperpolarized ➡️ This suppresses neurotransmitter release

-These receptors are selectively inhibited by **picrotoxin** and **bicuculline**, both of which are convulsants. These are chemicals not a drug, they are used in Research. If they inhibit sub form of GABA Channel then it is considered ionotropic receptor or Chloride Channel

- **GABAB** receptors are metabotropic receptors and are selectively activated by the antispastic drug baclofen.
- These receptors are coupled to G proteins, that either inhibit Ca2+ channels or activate K+ channels:

-Ca++ will enter the cells and will inhibit the other neuron (post synaptic neuron) by Preventing The release of neurotransmitter (Because regional transmitter needs Ca),
-K+ will leave the cell making it less positive inside/ hyperpolarization

Mechanism of action

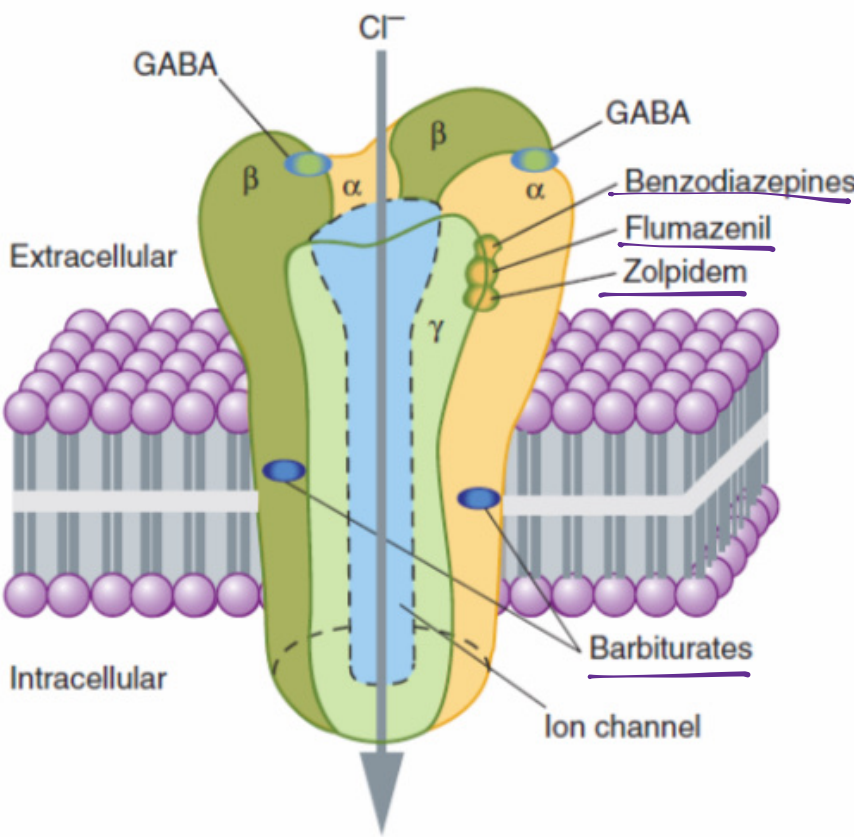
- The benzodiazepines, the barbiturates, zolpidem, zaleplon, eszopiclone and many other drugs bind GABAA receptors in neuronal membranes in CNS.

-They bind to the receptor and cause allosteric interaction that helps in opening the channels, but they don't work as replacement for GABA ,GABA Should be existed.

- They enhance its effects but are NOT agonists.
- Barbiturates binding site is different from that of the others.
- GABAA is a A hetero-oligomeric glycoprotein (Transmembrane receptor,)the complex consists of five or more membrane-spanning subunits.

-The arrangement of the subunits can be changed➡️ different sub types of GABAA Receptor.

A model of the GABAA receptor-chloride ion



- Multiple forms of α, β, and γ subunits (2α, 2β and 1 γ) are arranged in different pentameric combinations so that GABAA receptors exhibit molecular heterogeneity and Inside them we have the chloride channel
- GABA appears to interact at 2 site between alpha and beta subunits triggering chloride channel opening with resulting membrane hyperpolarization.
- Binding of benzodiazepines and the Newer hypnotic drugs such as zolpidem occurs at a single site between alpha and gamma subunits, Facilitating the process of the chloride ion channel opening.
- The benzodiazepine antagonist (**flumazenil**) also binds at this site and can reverse the hypnotic effects of zolpidem. Notice at the figure that these binding sites are distinct from those of the barbiturates. (Antagonist/antidote.
  - If the patient has excessive effect Or High dose of benzodiazepines , you give the patient flumazenil; because:
- 1) it's competitive to benzodiazepines and
- 2) The binding sites of Benzodiazepines and zolpidem are close to flumazenil binding site So flumazenil Can be used as Anti-dose for zolpidem too.
- The difference in their sites make the zolpidem hypnotic and benzodiazepines is hypnotic, anxiolytic and seductive
- barbiturates binds to 2 sites in transmembrane portion of the receptor Because allosteric change in the receptor will open it (one site in alpha and the other one in beta)

NOW, go back to the figure again and notice all the sites and subunits 💊💉

- Barbiturates also may depress the actions of the excitatory neurotransmitters (glutamic acid), and exert nonsynaptic membrane effects (like Ethanol)

-Ethanol works on many receptors in the body and has membrane effect, It is also considered a drug from class of sedative-hypnotic But shouldn't be used for this purpose

-and with Enhancing inhibitory neurotransmitter ➡️ more inhibition

- This makes them less selective than BDZs, have a more pronounced central depressant action and a low margin of safety (because Barbiturates have three mechanism of action while Benzodiazepines have one only)

1)barbiturates bind to GABA A receptors, enhancing GABA effect
2)barbiturates depress the action of excitatory neurotransmitters
3)exert nonsynaptic membrane effects

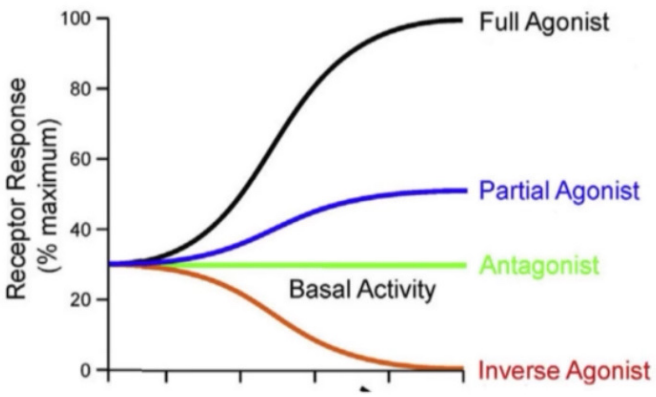
Drugs that inhibit the action of hypnotics :

1) **Flumazenil** (antidote) blocks the action of benzodiazepines, eszopiclone, zaleplon and zolpidem; but NOT barbiturates, meprobamate, or ethanol.
-Patients with ethanol abuse aren't treated with flumazenil, Treatment include opioid antagonist like naloxone or naltrexone.

2) **β-Carbolins** act as negative allosteric modulators (inverse agonists) of GABA-receptor function ➡️ anxiety and seizures. They also can block the effects of BDZs.
-this is a Natural alkaloids that exist in many plants
-Cause stimulation / Excitation of CNS

Difference between antagonist and inverse agonist :

-result is the same but the mechanism differs.
-Antagonist (competitive) bind to the receptor, block it and prevent the agonist from binding and perform its action
-Inverse agonist Binds to the receptor and produce different action from the natural agonist (different function)



This curve isn't required, just for more clarification

Pharmacological effects

Organ-System Effects:

1- **Sedation**:
• Calming effect with concomitant reduction of anxiety at relatively low doses.
• This effect may be accompanied by depressant action on psychomotor and cognitive functions.
-Specially Benzodiazepines and barbiturates, they affect cognition (impairment of cognitive function) , in addition to induce sleep ➡️ are the reasons why we don't give them to epilepsy person

2-**Hypnosis**:
• All of the sedative-hypnotics induce sleep if enough doses are given.
• The use of sedative-hypnotics for more than 1-2 weeks leads to tolerance to their effects on sleep patterns (if The patient uses them continuously).

3-**Anesthesia**:
• Thiopental and methohexital are very lipid soluble, penetrate brain tissue rapidly after IV administration, and are useful for induction of anesthesia.

• Rapid tissue redistribution accounts for their short duration of action.

-Other anesthetic agents take longer time to produce effect, So balance anesthesia gives the patient a potent analgesic so he/she doesn't feel the pain + thiopental to sleep immediately. After 4 to 5 minute other drugs work and Rule of thiopental ends.

-note:Remember: We mentioned that termination of action does not depend on the half life, it depends on the redistribution

- Benzodiazepines may be used IV in anesthesia in combination with other drugs Or as a premedication before taking the patient to the Operating room, but aren't used alone to induce sleep during anesthesia.
- If used at large doses, they can produce post-anesthetic respiratory depression (because it's an active metabolites and has long t½), which can be blocked by flumazenil (should be prepared to reverse the action of Benzodiazepines)

4-**Anticonvulsant effects**:
• Many sedatives-hypnotics are capable of inhibiting the development and spread of epileptiform electrical activity in the CNS (like Phenobarbital).

• Some selectivity exists in that anticonvulsant action is not associated with marked CNS depression, but psychomotor function may be impaired.

• Several benzodiazepines – clonazepam, nitrazepam, lorazepam and diazepam – are sufficiently selective to be used as anticonvulsants. (acutely)
-Can terminate an attack by giving them IV, you can't wait for it to end because it might take time and the patient might get injured (bite his tongue), it's almost effective immediately.

• Phenobarbital is effective in the management of generalized tonic-clonic seizures. (long-term use)

- Zolpidem, zaleplon and eszopiclone lack anticonvulsant activity, probably because of more selective binding to GABAA receptor isoforms than that of benzodiazepines

5-**Muscle relaxation**:
-Centrally mediated muscle relaxation(Central origin spasm/ from brain))
• Some sedative-hypnotics, meprobamate and benzodiazepines, exert inhibitory effects on polysynaptic reflexes (Not barbiturates).

• Muscle relaxation is NOT a characteristic action of zolpidem, zaleplon, and eszopiclone

6-**Effects on respiration**:
• Sedative-hypnotics, even at therapeutic doses, can produce significant respiratory depression in patients with pulmonary diseases.

• Respiratory depression is dose-related, and can be the cause of death with overdose.
-Especially dangerous if the patient has any respiratory problem (Bronchial asthma, chronic obstructive pulmonary disease, obstructive sleep apnea), Never give them sedative hypnotic drugs because it will Induce respiratory centre depression and kill them

• Respiratory effects are more marked after IV administration
-IV administration of a drug will depress the respiratory center even more because it gives higher initial concentration of the drug, Oral administration gives moderate concentration of the drug. If we must use them we can't give them by IV

7-**Effects on cardiovascular function**:
• May depress CVS as a result of depression of the medullary vasomotor center in hypovolemic states and when cardiac function is impaired.
-Suppress the Vasomotor center

• With overdose, myocardial contractility and vascular tone may be depressed leading to circulatory collapse.

• Cardiovascular effects are more marked after IV administration

The next 2 slides weren't explained by the doctor in the lecture

◯ Tolerance; Psychologic and Physiologic Dependence:

Tolerance is a common feature of sedative-hypnotic use.
• Partial cross-tolerance occurs among the sedative-hypnotics and also with ethanol.
• An increase in drug metabolism may be contribute to tolerance with barbiturates.
• Changes in the responses of the CNS are of greater importance (pharmacodynamic tolerance).
• With benzodiazepines, it may be due to down regulation of brain BDZ receptors.
• Tolerance can occur with extended use of zolpidem, but much less so with zaleplon and eszopiclone

ذكر ابن الجوزي رحمه الله: تاللهِ لو قِيلَ لأهلِ القُبورِ تَمَنَّوا التَمَنَّوا يومًا من رمضان."

كل عام وأنتم بخير ❤️