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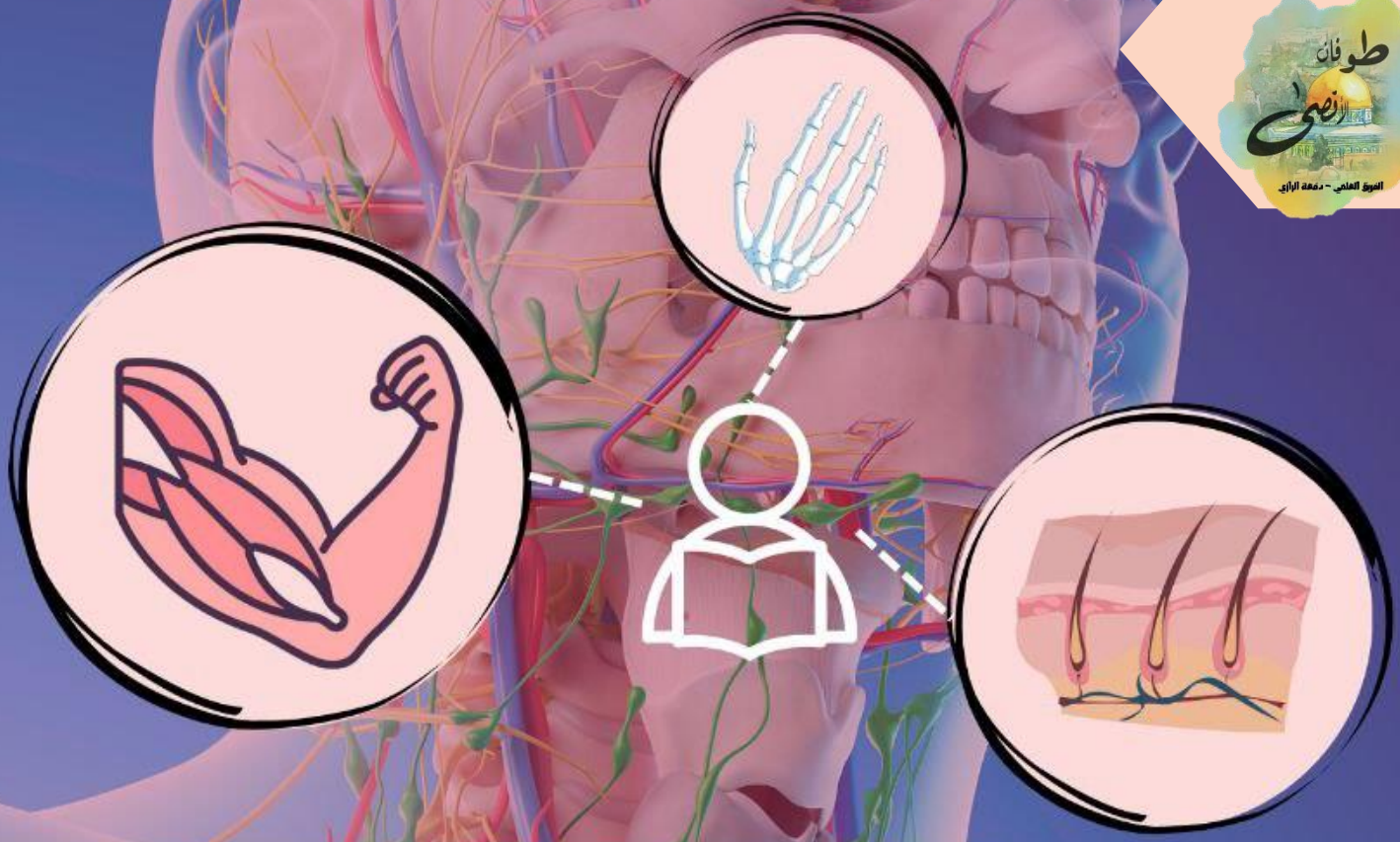

Pharmacology

Sheet no. 4

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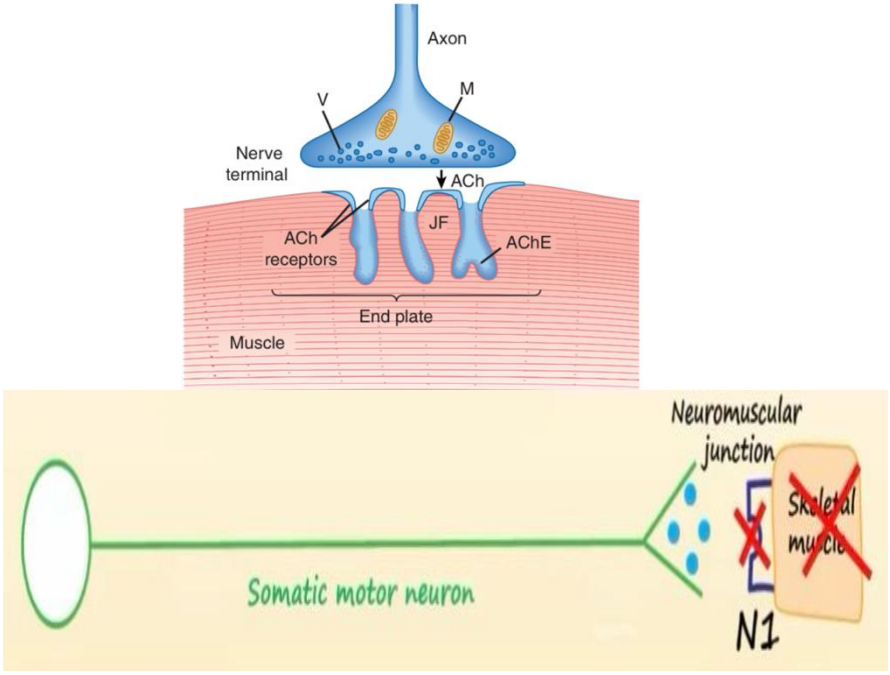
Muscle Relaxants 2

Our pharmacology topic is muscle relaxants. Muscle relaxants decrease muscle tone and are used to treat symptoms associated with increased muscle tone, such as muscle spasms (involuntary painful contractions of one or more muscles), hyperreflexia (loss of inhibitory modulation of the motor pathways which results in overactive bodily responses) and pain. Technically the term muscle relaxants can be subdivided into two major groups, including neuromuscular blockers and spasmolytics.

<u>Neuromuscular blockers</u> work in the periphery by blocking nicotinic 1 receptors "N1 or Nm" in the neuromuscular junction to stop skeletal muscle contractions (and lack central nervous system activity). They are useful during certain types of surgery and for procedures such as intubation (a procedure that's used when you can't breath on your own by relaxing the pharyngeal and laryngeal muscles) to cause short-term flaccid paralysis.

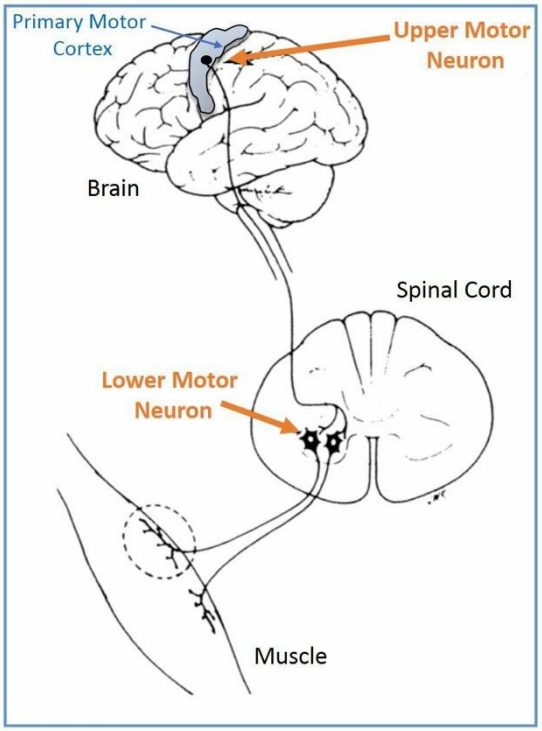


Neuromuscular spasmolytics work centrally at the level of the spinal cord or brain. The term muscle relaxants is most often used to refer just to spasmolytics, and these are the topic of this video. Remember that an indication is the reason the drug is used.
As mentioned, muscle relaxants (neuromuscular spasmolytics) are often indicated for the treatment of painful musculoskeletal conditions. Some examples include treating muscle spasms associated with overexertion and helping manage the spasticity of severe chronic disorders like multiple sclerosis and cerebral palsy (a neurological condition that can present as issues with muscle tone, posture and/or a movement disorder). These drugs usually work best when used alongside physical therapy.

*Spasticity is characterized by an increase in tonic stretch reflexes and flexor muscle spasms (ie, increased basal muscle tone) together with muscle weakness.

Before we start with the mechanism of action of spasmolytics, let's revise some neurophysiology.

A motor neuron is a type of neuron that carries information from the brain or spinal cord and is involved in regulating activity in muscles or glands. There are 2 types of motor neurons: 1. Upper motor neurons (UMN) 2. Lower motor neurons (LMN). They interact with each other to cause movement and other responses.

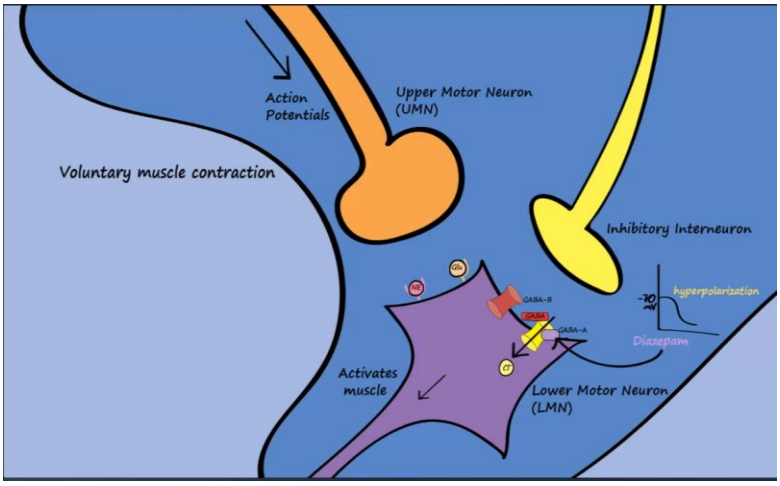


Upper motor neurons originate in multiple areas of the brain and brainstem and carry information about desired movements or other responses in descending tracts. Upper motor neurons descend to various levels of the brainstem and spinal cord and form connections with lower motor neurons, lower motor neurons then influence the activity of muscles or glands.

Now let's get back to pharmacology,

1. **Diazepam: For voluntary muscle contraction of limbs, the upper motor neuron, or UMN, is activated in the cerebral cortex and action potential travels down the spinal cord where they synapse with lower motor neurons, or LMNs, at the level of exit. Inhibitory interneurons regulate the excitation of the LMNs, and action potential traveling down the upper motor neuron will cause the release of excitatory neurotransmitters, like norepinephrine or glutamate, onto the LMN, which will then activate the skeletal muscle. The inhibitory neurotransmitter GABA is released from the inhibitory interneuron and acts to decrease the excitation of the LMN by increasing chloride permeability in the LMN(hyperpolarzation).**

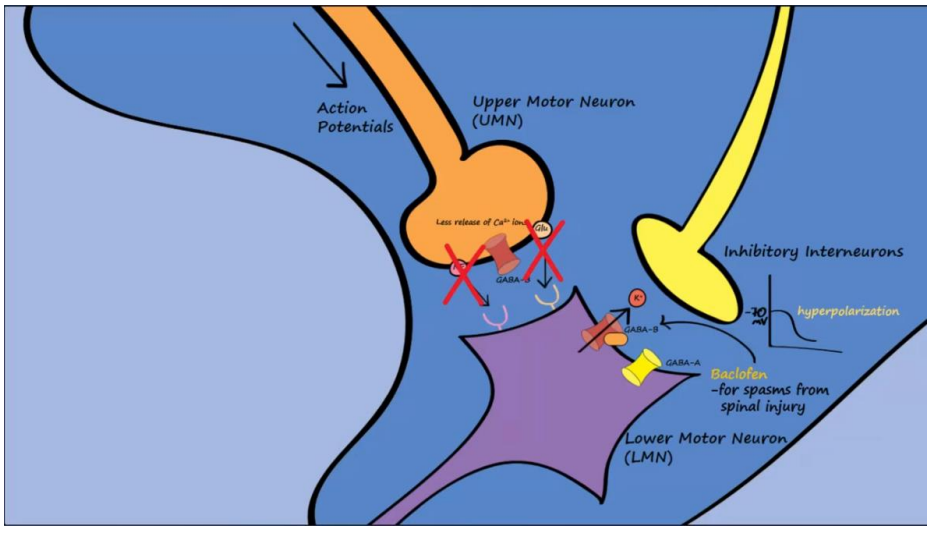
Diazepam, a drug of the benzodiazepine family "BZD" used for muscle spasms, will bind to the BZD binding site on GABA A receptors



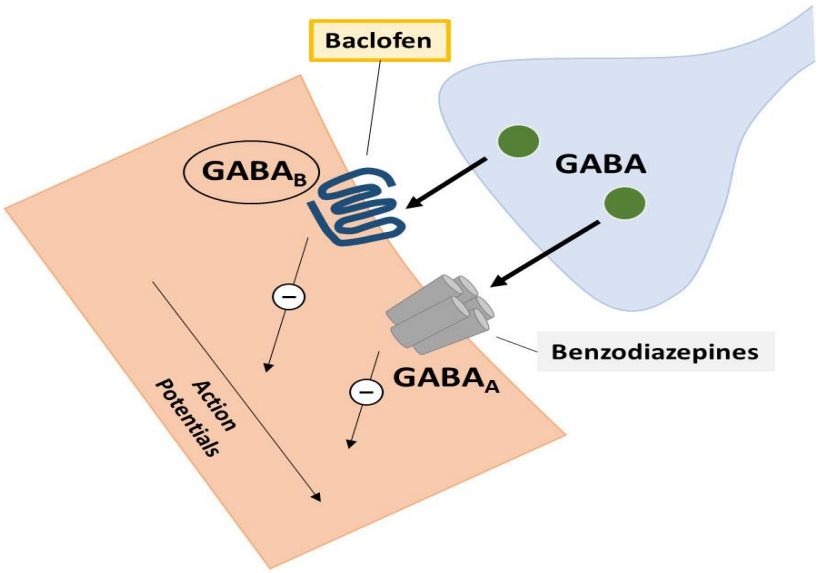
located on cell bodies of the lower motor neurons to increase the permeability of chloride even more.

Thus, the action of diazepam augments or increases the action of GABA and hyperpolarizes the cell even more. Hyperpolarization decreases the frequency of action potentials traveling through the LMN to the muscle.

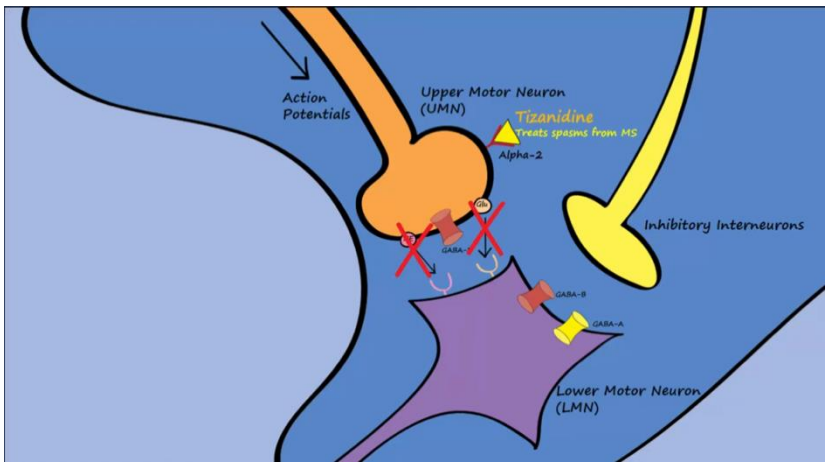
2. **Baclofen: it's a drug used for spasms associated with spinal cord injuries. Baclofen activates GABA-B receptors in the postsynaptic membrane to cause an increase in potassium conductance in the LMN, which also causes hyperpolarization. There are also GABA-B receptors in the presynaptic membrane of the upper motor neuron. Activation of these receptors leads to less release of calcium ions and, consequently, less release of excitatory neurotransmitters, like norepinephrine and glutamate from the UMN onto the LMN. Consequently, less action potentials travel down the LMN to reach the muscle.**



A comparison between Diazepam and Baclofen



3. **Tizanidine, it's one of the drugs used for spasms associated with multiple sclerosis. This drug is an alpha-2 agonist and binds to UMN axon terminals and causes less release of excitatory neurotransmitter.**

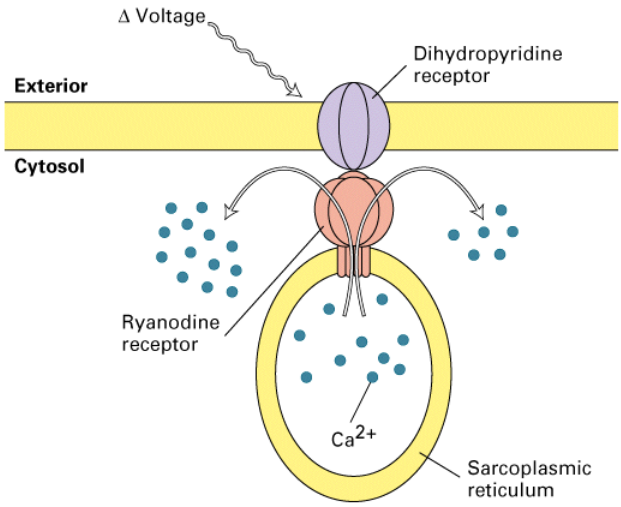


4. **Dantrolene, is a direct-acting muscle relaxant that blocks ryanodine receptors in skeletal muscles. Therefore, unlike the other muscle relaxants, it doesn't act in the CNS. Dantrolene is**

indicated for the treatment of muscle spasms associated with multiple sclerosis, cerebral palsy, spinal cord injuries and MH(Malignant hyperthermia).

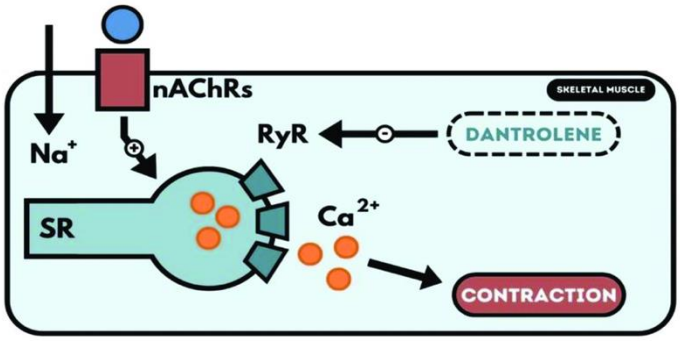
A special application of Dantrolene is in the treatment of malignant hyperthermia, a rare severe reaction characterised by fever, muscle rigidity, tachycardia. although rare MH occurs in susceptible individuals who are exposed to general anesthetics (eg, volatile anesthetics like halothane) and depolarizing neuromuscular blocking drugs (succinylcholine). Patients at risk for this condition have a hereditary alteration in Ca-induced release via the RyR1 channel or impairment in the ability of the sarcoplasmic reticulum to sequester calcium.

Dantrolens reduces skeletal muscle strength by interfering with excitation-contraction coupling in the muscle fibers. The normal contractile response involves release of calcium from its stores in the sarcoplasmic reticulum .
This activator calcium brings about the tension-generating interaction of actin with myosin. Calcium is released from the sarcoplasmic reticulum via a calcium channel, called the ryanodine receptor (RyR) channel.



Dantrolene binds to the Ryanodine Receptor Channels (RyR1) and prevents it from opening when the action potential reaches the DHPR. This prevents release of calcium from the sarcoplasmic reticulum and prevents muscle contraction.

Dantrolene is more selected for skeletal muscle because the heart has ryanodine type 2 receptors (RyR2) instead of type 1 that is in skeletal muscle.



MOAs for spasmolytics:

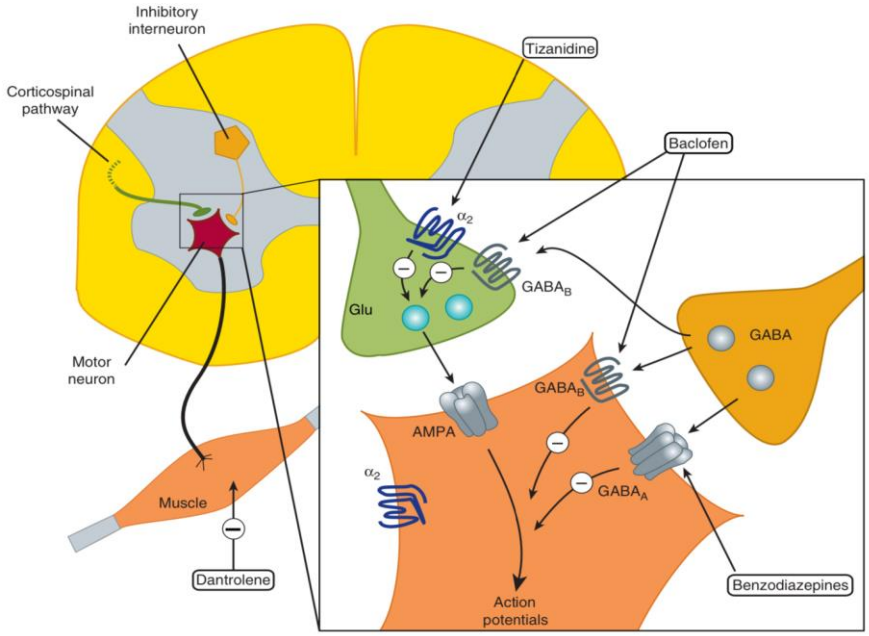


FIGURE 27–11 Postulated sites of spasmolytic action of tizanidine (α_2), benzodiazepines ($GABA_A$), and baclofen ($GABA_B$) in the spinal cord. Tizanidine may also have a postsynaptic inhibitory effect. Dantrolene acts on the sarcoplasmic reticulum in skeletal muscle. Glu, glutamatergic neuron.

Drugs for Local Muscle Spasms:

Several muscle relaxers are used for acute local muscle spasms associated with overexertion or injuries. Manual laborers, or those in car accidents, are examples of individuals who may have these drugs prescribed by a physician. Common muscle relaxers that fit

this category are carisoprodol, cyclobenzaprine, metaxalone, corzoxazone, and orphenadrine, they are promoted for the relief the acute muscle spasm caused by local tissue trauma or muscle strains.

The mechanism for these drugs is not well understood, but is believed that they act in the brainstem. Muscle relaxers that act in the CNS have the following adverse effects in common: euphoria (elevated mood), lightheadedness or dizziness, fatigue, and muscle weakness. Due to these effects, it is important to advise patients and monitor them while taking these medications. Also, since most muscle relaxers are CNS depressants, don't mix with alcohol and use caution when driving and operating machinery.

Summary of Muscle Relaxers Mechanisms of Action:

- **Dantrolene ~ Blocks Ryr1, receptors in skeletal muscle**
- **Diazepam ~ Augments GABA-A receptors to increase Cl- permeability**
- **Tizanidine ~ Alpha-2 agonist that decreases release of excitatory neurotransmitters**
- **Baclofen ~ Augments GABA-B receptors to increase potassium permeability**

- **carisoprodol**
- **cyclobenzaprine**
- **metaxalone**
- **chlorzoxazone**
- **orphenadrine**

Not well understood mechanism, but believed to act in the brainstem.

Which statement/s regarding muscle relaxants is/are accurate?

A. **Baclofen is a peripherally acting neuromuscular blocker.**
B. **Cyclobenzaprine produces no sedation.**
C. **Tizanidine increases chloride permeability by augmenting the actions of GABA.**
D. **The Ryr1, receptor is located in the cell bodies of lower motor neurons.**
E. **2 of the above (A through D) are correct**
F. **3 of the above (A through D) are correct**
G. **4 of the above (A through D) are correct**
H. **None of the above are correct**

Ans: H

Good Luck !

اللهمَّ كُن لأهلنا في غزَّة

اشفِ جريحهم، وتقبل شهيدهم، وأطعِم جائعهم، وانصرهم على عدوّهم. اللهم أنزِل السكينة عليهم، واربط على قُلوبهم، وكُن لهم مُؤيدًا ونصيرًا وقائدًا وظهيرًا. سُبحانكَ إنَّك على كُل شيءٍ قدير؛ فاكتب الفرج من عِندك والطف بعبادك المُؤمنين، اللهم اغفر لنا تقصيرنا وأعط أهل غزة من خيري الدنيا والآخرة ما تقر به أعينهم