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Midazolam and How Physiologic Changes in the Elderly Patient's Body Lead to Adverse Effects

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Introduction:

One of the most important medical advances in the last two-hundred years has been the development of anesthesia. Out of all the milestones and achievements in medicine, anesthesia is quite possibly one of the few that has the potential to affect every individual in the world (1). Anesthetics have opened up a new door in the medical field, and have allowed for the performance of contemporary, progressive surgeries that physicians would never have been able to accomplish before. Anesthesia has effectively allowed for safer and more efficient medical practices to take place.

An anesthetic is classified as any type of drug that promotes a temporarily induced loss of sensation or awareness. The function of an anesthetic may include relief or prevention of pain, muscle relaxation, loss of memory (amnesia), unconsciousness, and reduction of anxiety (anxiolytics). Essentially, anesthesia enables the otherwise difficult performance of surgery that would certainly make the patient feel extremely uncomfortable. There are three main forms of anesthesia: general, regional, and local. General anesthesia is usually administered intravenously or through inhalation, and the goal of this type of anesthetic is to keep the patient completely unconscious during the procedure. Regional anesthesia is administered near a cluster of nerves and effectively numbs a large area of the body without making the patient unconscious. Local anesthesia only numbs a small, specific area of the body and lasts for a short period of time. Both regional and local anesthetics can be used in combination with general anesthesia to limit the amount of pain felt during and immediately after a procedure (2).

Various forms of anesthesia have existed since 4000 B.C., but the birth of modern anesthesia occurred in 1846 when Dr. William Morton successfully administered ether to a patient at Massachusetts General Hospital (1). Since then, as medicine has progressed, many different types of anesthetic drugs have been discovered and successfully used in the form of inhalants, intravenous agents, and local/topical anesthetics. As stated earlier, anesthetics have properties that promote pain relief, sedation, amnesia, anti-anxiety, and muscle relaxation. One such type of anesthetic that encourages all of these effects are benzodiazepines (3) Benzodiazepines were accidentally first discovered in 1955 by the chemist Leo Sternbach while he was working for the healthcare company Hoffman-LaRoche on the development of tranquilizers. The initial clinical findings of benzodiazepines were impressive, and now, benzodiazepines are commonly used in various medical procedures today (4).

Benzodiazepines are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. A benzene ring is a six carbon molecule, in which there is a double bond between every other carbon while a diazepine ring is a seven member ring that contains five carbon atoms, two nitrogen atoms, and three double bonds (Figure 1). The addition of specific R groups, or side chains of different atoms, to this core structure give benzodiazepines their different properties and functions, and since the basic structure of benzodiazepines contains four distinct R groups (R1, R2, R2', and R7), there can be significant variety between different drugs in this class of anesthetics. Based on the R group substituents, five different pharmacological subgroups of benzodiazepines have been defined: the alpha-keto benzodiazepines, the 3-OH benzodiazepines, the 7-nitro benzodiazepines, the triazolo benzodiazepines and the imidazo benzodiazepine (midazolam). The alpha-keto benzodiazepines all have a ketone substituent group attached to the diazepine ring and are associated with anti-

anxiety. The 3-OH benzodiazepines all have a hydroxyl (-OH) group attached to the third carbon in the diazepine ring as well as a ketone group, and this means that this subgroup is linked with anti-anxiety and sedation. The 7-nitro benzodiazepines have a nitrogen dioxide group attached to the fused benzene ring, and drugs of this subset are related to the relief of anxiety. The triazolo benzodiazepines all commonly share a triazole group that is attached to the diazepine ring, and are associated with sedation. Lastly, midazolam is in a class of its own and contains an imidazole group that is connected to the diazepine ring (Figure 2). Midazolam helps with sedation and amnesia.

Benzodiazepine derivatives in the same subgroup are metabolized by similar mechanisms since they contain comparable R groups. Therefore, these derivatives have similar half-lives, which is amount of time that a particular drug stays within a patient's system. However, benzodiazepines with similar chemical structures can differ tremendously in their potency, rate of absorption, and other pharmacological parameters. Differences in potency depend on the particular combination of R group substituents at various positions. These distinct R groups also affect how the benzodiazepine travels throughout the body and its ultimate mechanism of action (5).

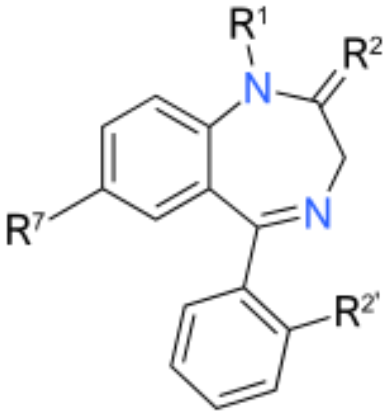

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Figure 1. Basic Structure of Benzodiazepine

Benzodiazepines are revered in medicine for their sedative, anxiolytic, and amnesic properties, and they are commonly used in a wide variety of procedures. Amnesia is considered an important property of benzodiazepines since it helps patients forget the events surrounding a surgery (6). The most common benzodiazepines in use today are midazolam, diazepam, and lorazepam. All the effects of benzodiazepines, such as the ones listed above, result from their actions on the neurotransmitter, or chemical messenger, gamma-aminobutyric acid (GABA), specifically at the $GABA_A$ receptor in the central nervous system, which is a particular receptor class of GABA (7). Benzodiazepines produce a sedative effect because they facilitate the binding of GABA to the $GABA_A$ receptor, which hinders the flow of electrical impulses in the brain. Benzodiazepines allosterically bind to the $GABA_A$ receptor which helps to increase the effects that GABA provides. The $GABA_A$ receptor is involved in, and regulates, the majority of fast inhibitory neurotransmission in the vertebrate brain, and as a result, is involved in drug response since benzodiazepines produce a calming, sedative effect (8). In summary, benzodiazepines enhance the effects of GABA by helping GABA bind to its receptor so the neurotransmitter can illicit its inhibitory effects.

Benzodiazepines are used on a wide variety of patients for the favorable anesthetic and pharmacological effects they produce. Patients of the elderly population are at most risk of developing adverse side-effects from benzodiazepines. Significant functional deterioration, meaning the loss of the ability to function unassisted, has been frequently observed after surgery in elderly patients, and some of these cases may relate to the use of benzodiazepines as an anesthetic. Essentially, temporary loss of memory from surgery can disrupt the fine balance between independence and disability in geriatric patients. This loss of memory can erode any self-confidence, which can lead to depression, noncompliance, and morbidity in the elderly. In this case, the relatively minor and well-recognized effect of benzodiazepines on the memory can result in serious consequences (6).

Old age may lead to altered pharmacokinetics, which refers to the movement of drugs within the body, and pharmacodynamics, which refers to the mechanism of action of drugs and their effects in the body, of these anesthetics. The altered physiology of these elderly patients have been found to cause altered clinical responses to sedative-anxiolytic drugs such as benzodiazepines. Relative to younger individuals, higher plasma concentrations of benzodiazepines are witnessed in geriatric patients after single or multiple doses of these drugs. This higher plasma concentration of benzodiazepines tends to be because advanced age is associated with impaired clearance of these psychoactive drugs. This impaired clearance is due a reduction in liver and kidney function and a decrease in serum albumin levels. Benzodiazepines also have a half-life that is almost double in geriatrics when compared to younger patients. These longer half-lives have shown increased incidence of adverse side effects such as confusion and memory loss in elderly patients. An increase in age may also lead to an increased intrinsic sensitivity to benzodiazepines. This means that the elderly have an increased response at any

given plasma concentration compared to younger individuals. Increased benzodiazepine sensitivity has been documented in clinical use and in laboratory trials and shows that the altered pharmacodynamics and pharmacokinetics of geriatric patients can lead to a heightened effect of benzodiazepines on their bodies (9).

Midazolam is the most commonly used benzodiazepine in medicine today because of its high potency, short half-life, and lipid and water solubility. The structure of midazolam consists of an imadazole group with a methyl group attached in the R1 and R2 positions, a fluoride group in the R2' position, and a chloride group in the R7 position (Figure 2). Midazolam is considered its own class of benzodiazepine since it contains an imidazole group that is connected to the diazepine ring. The imidazole group is what gives midazolam its amnesic property. Enhanced responses in the elderly body due to this drug can be attributed to an age-related changes in the subunit makeup of the $GABA_A$ receptor (6). These responses can also be a result of physiological changes, such as alterations in body and organ makeup, variations in receptor number and receptor-drug affinity, signal transduction, and homeostatic mechanisms that occur as the body ages and are what cause the elderly to be more likely to have adverse side effects to midazolam and other benzodiazepines when compared to younger, healthier patients (10).

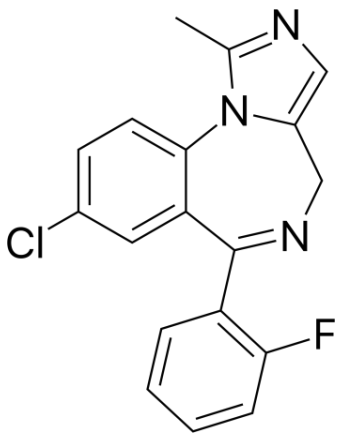

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Figure 2. Structure of Midazolam

The increased pharmacodynamic, pharmacokinetic, and physiologic responses in the elderly are important to fully understand why these types of individuals experience effects from midazolam that are exceptionally profound. Changes in body and organ composition and receptor makeup of a geriatric patient are crucial to figuring out why these responses occur. The overall goal is to determine how and why the elderly are more sensitive and susceptible to the effects that midazolam produces. It is important to comprehend why these side-effects occur because the elderly account for about 11% of the population that undergo surgery on a yearly basis (11). Also, by 2050, the worldwide population aged over 65 years is projected to increase from 6.9% of the total population to 15.9%, which constitutes an extra billion elderly individuals. With midazolam being one of the most reliable anesthetics used in medical procedures today due to its high potency and fast rate of reaction, it is imperative to resolve why midazolam can adversely affect the elderly so that safer medical practices can be developed.

Literature Review:

Midazolam is one of the most common anesthetics in use today because it is revered for both its lipid and water solubility, short half-life, and greater potency when compared to other

benzodiazepines (12). As revered as midazolam is for its sedative, anxiolytic (anxiety reducing), and amnesic properties, elderly patients have been found to have altered clinical responses to this type of drug. This is because physiological changes such as changes in receptor and protein number and affinity, organ makeup, and body mass, as the result of aging, lead to enhanced pharmacokinetic and pharmacodynamic responses in the geriatric patient's body. These increased responses are what cause the elderly to be more likely to have adverse side effects to midazolam that are more profound when compared to younger, healthier patients, and these adverse side effects include prolonged amnesia, hysteria, functional deterioration, and depression. These side effects can be crippling to someone of the elderly community and can lead to a severe loss of self-confidence that they may never be able to fully recover from since it can leave them questioning the world around them. This can greatly diminish their independence and drastically effect their way of life after a simple, routine surgery.

Pharmacokinetic Changes -

Midazolam is considered a short acting benzodiazepine and usually has a duration of action of about three to four hours, which is the amount of time that midazolam has a pharmacological effect on the body (13). Midazolam also has a short distribution half-life (the time taken for 50% of the drug present in plasma to distribute outside the bloodstream) of four to nineteen minutes, and this is favorable since its effects are seen relatively quickly in the patient (14). These characteristics and properties of midazolam are important in the pharmacokinetic aspects of the geriatric patient when comparing them to the younger population. Pharmacokinetic changes that occur in elderly patients are changes in total body makeup, changes in drug metabolism and excretion, and changes in plasma protein numbers. Total body makeup changes in the geriatric patient include a decrease in total water volume, an increase in total body fat, and

a decrease in total muscle mass. Aging is accompanied by an increase in body fat of 25-30%, a decrease in lean body mass and a decrease in total body water volume. Since drug distribution depends largely on body composition, these changes result in reduced volume of distribution of water soluble drugs, which may lead to increased initial drug concentration, and increased volume of distribution of lipid soluble drugs, such as benzodiazepines, which may lead to increased elimination half-life and prolonged effect (15).

However, midazolam has the ability to be both a water-soluble and lipid-soluble drug depending on the pH of its environment. If the pH of the enviroment is less than 4, midazolam will exist as a water soluble drug. If the pH of the environment is greater than 4, midazolam will exist as a lipid soluble drug (16). This means that midazolam is able to have both an increased initial drug concentration and an increased elimination half-life. Therefore, if midazolam is given orally, it will exist as a water-soluble drug in the stomach and gastrointestinal tract since the pH of the digestive system is usually at around a pH of 4.0. Since there is less water present in the elderly patient's body, the concentration of midazolam will be higher than it would be if the same dosage was given to a younger patient. If midazolam is given intravenously, it will exist as a lipid-soluble drug since the pH of the blood is around 7.35 and this will mean that midazolam will concentrate in fatty tissues. The increased presence of body fat in the geriatric patient allows for more midazolam to distribute throughout the body. This would cause more of the drug to be present in the elderly patient's body for a longer period of time. Other literature agrees and states that drug distribution in the elderly may be altered by significant changes in the lipid to lean body mass ratio (17). It was also mentioned in the literature that increased fat in the geriatric patient increases the volume of distribution for highly lipophilic drugs such as benzodiazepines

and may increase their elimination half-lives which would lead to the drug staying in the body and producing a more profound effect than was originally anticipated (18).

Serum Albumin and Aging -

The number of plasma proteins available also effects the drug distribution of midazolam. Serum albumin, a protein found in blood plasma, plays an important role in binding midazolam and transporting it throughout the body and the amount of serum albumin available effects the free drug concentration (i.e., the amount of drug that is not bound to protein in the serum). This population of unbound drug molecules is able to exert the therapeutic or toxic effect of the drug that is administered. The term "free fraction" is used to describe the percentage of the drug that is unbound in the serum versus the total drug concentration. In the elderly, as age increases, the amount of serum albumin protein that is present in the blood decreases. This decrease can result in an increase in the free fraction of drugs that are usually highly bound to albumin when they are first administered to a patient until their steady-state equilibrium is established, and this leads to more unbound midazolam that is able to exert its effects on the patient. Essentially, the less serum albumin that is present in a patient's blood, the more drug that is available to produce adverse effects on the patient and just a small reduction in protein binding may result in a clinically significant increase in free drug concentration (15).

There are two different opinions when it comes to the effects of drugs such as benzodiazepines and the reduction of serum albumin. The first hypothesis is that serum albumin levels decrease normally with age. This is demonstrated in a study on elderly patients who did not possess disease states such as dysproteinemia and malnutrition, which are potentially associated with abnormal serum albumin levels (19). Of the patients in the study, the mean serum albumin concentration fell progressively with each decade of age, from 3.97 g/dL in

subjects aged less than 40, to 3.58 g/dL in those aged 80 or older (19). The percentage of patients with a normal serum albumin level (4.0 g/dL or higher) also decreased progressively with age, whereas the frequency of a low serum albumin level increased with age (19). There is also agreeance in the scientific literature that serum albumin levels decrease as a result of the normal aging process (20). A study showed that serum albumin levels decreased with age in both men and women. In the study that they performed, the median value declined from 4.3 g/dL in males aged 65-69 to 3.9 g/dL in 90 or greater, and 4.3 g/dL to 4.0 g/dL in females. Incidence of hypoalbuminemia (when serum albumin is less than or equal to 3.5 g/dL) increased in parallel with age from 1.2% in elderly aged from 65-69 to 6.6% in males aged from 85-89, and 0.6% to 4.1% in females (20). It was concluded that a fall in serum albumin concentration in community-dwelling, self-supported (healthy) elderly persons was associated significantly with aging (20).

However, there is some scientific literature that disagrees with the fact that decreased serum albumin levels are strictly reliant on the normal aging process. This literature believes that reduced serum albumin levels are associated with disease, and the elderly's greater susceptibility to disease explains why they tend to have decreased albumin levels compared to the younger population. One source of literature stated that disease may reduce albumin in any age group, and studies have shown no association between age and albumin (21). To investigate the association of age and albumin, albumin levels were determined in 241 apparently healthy subjects aged 55 to 101. A small but consistent negative regression slope of about 4% per decade was found for those aged over 70. From the results, both concluded that hypoalbuminemia in elderly patients generally should be attributed to disease rather than age alone (21). Other scientific literature also had similar findings to show that decreased serum albumin levels are not just a result of the normal aging process. To clarify the relation between age and serum albumin

levels, a population of 1066 healthy males was screened (22). The results of the study showed only a slight decline in albumin of 0.054 g/dL per decade. This small decline occurs entirely within the range of normal (3.5-5.5 g/dL), contrary to many reports. Mean albumin values were 4.25 g/dL for patients in their eighties and 4.13 g/dL for patients in their nineties (22). This led to the conclusion that the age-related decline within healthy subjects is far less than previously described, and the data from the study demonstrated that hypoalbuminemia is not a consequence of normal aging (22). The disagreements between how serum albumin levels are affected by age are still up for debate. However, it can be agreed upon that reduced serum albumin levels in the blood lead to more adverse effects from drugs such as midazolam so the disagreements on how serum albumin levels decrease seems to be trivial.

Liver Function and Aging -

Drug metabolism and excretion also change as aging occurs. The metabolism of medications primarily occurs in the liver, and a decrease in mass of the liver, coupled with a decrease in function, plays an important role in the reduction in drug metabolism in the elderly patient. The liver mass in a patient of advanced age reduces by 20% to 40% and is accompanied by a 35% decrease in hepatic blood flow when compared to an individual who is younger and healthier. As a result of this reduction in mass and volume of blood flow, medications will show a higher bioavailability in a geriatric patient (10). Other literature agrees with this and states that liver metabolism is comprised of phase 1 reactions (oxidation, reduction and hydroxylation, largely performed by oxidases such as cytochrome P450) and phase 2 reactions (conjugation) (Figure 3). Phase 2 reactions appear to be unchanged by the aging process, however, phase 1 reactions are reduced due to a combination of reduced hepatic blood flow and reduced hepatic blood volume. This is because phase 1 enzymes are more oxygen dependent than phase 2

enzymes, and if less blood is flowing through the liver then that means less oxygen is able to enter the liver as well. The result is that drug metabolism, particularly phase 1 metabolism, may be considerably reduced in elderly people (15). More literature has a similar view that drug metabolism in the elderly is impaired because of a decrease in liver mass and a decrease in hepatic blood flow (23). A study was performed and it was found that there are no significant differences in cytochrome P450 3A4 (CYP3A4) activity between young and old populations. CYP3A4 is an enzyme that is found in the liver, and it is responsible for the phase 1 metabolism of midazolam so that it can be removed from the body. Other scientific literature also backed this research by showing that aging has no effect on CYP3A4 metabolic clearance of midazolam (24). This means that the function of hepatic enzymes do not decrease with age, and continue to function normally.

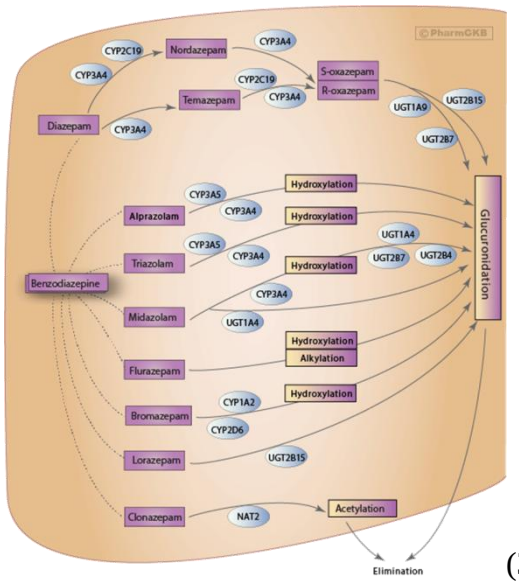

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Figure 3. Diagram of Midazolam Metabolism in the Liver

However, other scientific literature found that CYP3A4 metabolic activity did decrease as a result of aging, and this was demonstrated in a study where lignocaine, a drug metabolized by

CYP3A4 just like midazolam, was administered to young and elderly patients (25). It was found that CYP3A4 took longer to metabolize the lignocaine in the elderly patients than in the younger patients. Other literature contributes to this debate by stating that investigations on the influence of aging on phase 1 enzymes in humans have reported conflicting results. It was concluded that a study conducted in 54 liver samples from healthy donors from 9 to 89 years did not show changes in either microsomal protein content or total cytochrome P450 enzyme activity with age. By contrast, another study carried out on 226 subjects revealed a significant decrease of 32% in total cytochrome P450 content of liver biopsy samples (26). This means that the less liver enzymes that are present in the liver leads to less midazolam that is able to be metabolized. This in turn means that less midazolam is able to make it to the kidney for excretion. Therefore, there are conflicting views as to why reduced liver drug metabolism occurs in the elderly, but a decreased metabolic drug rate is caused nevertheless and, as a result, leads to midazolam having a longer, more implicit effect on the elderly patient since the drug stays in the patient's system much longer.

After reviewing the literature further, it is consistent in stating that a decreased metabolic rate of midazolam by the liver is caused by a reduction in liver mass and the subsequent reduction of hepatic blood flow and hepatic blood volume. As stated earlier, enzymes involved in phase I metabolism in the liver are very oxygen dependent and the less blood that is able to flow through the liver means that less oxygen is able to enter the liver as well. This would make it appear that the activity of phase I enzymes such as CYP3A4 are being decreased when in reality they are not, and the blood is just flowing through the liver at a slower rate (27). This decreased rate of blood flow and a reduced volume of blood entering the liver causes midazolam to not be metabolized as quickly and this leads to a greater availability of active midazolam in the elderly

patient's bloodstream which can lead to a potentiated effect since midazolam is not able to be converted into non-active metabolites. Therefore, aging does not affect metabolic enzymes and their activity such as CYP3A4 and only affects the physiological aspects of the liver which lead to midazolam having a greater bioavailability.

Kidney Function and Aging -

Drug excretion via the kidney, or renal excretion, also decreases in the elderly patient, and the half-life of drugs in an elderly patient's body is increased as renal function is reduced. This decline in renal function is the result of several physiological changes, which include a reduction in blood flow to the kidneys, a decrease in kidney mass, and a reduction in the size and number of functioning nephrons (28). A nephron's chief function is to filter the blood, eliminate wastes from the body, regulate blood volume and blood pressure, control levels of electrolytes and metabolites, and regulate blood pH. A reduction in the glomerular filtration rate (GFR) of the kidneys is also a consequence of aging (28). GFR refers to the amount of blood that is able to pass through the glomeruli of the kidney, and the glomeruli are tiny capillaries located at the beginning of the nephron in the kidney which serve as the first step of blood filtration. Scientific literature sources are in agreement with the statement about decline in renal function and, through research and data, suggest that the most important pharmacokinetic change in the elderly is the reduction in renal drug elimination as glomerular filtration rate, tubular secretion, and renal blood flow are reduced. This was shown by the reduction in inulin clearance as aging occurs and the more elderly a patient was, the less inulin was able to be cleared by the kidneys. Inulin is a substance that is neither absorbed or excreted by the body, and, as a result, is great for examining the GFR and function of the kidneys (29, 30). A decrease in blood filtration leads to less midazolam that is excreted from the body and, as a result, more midazolam is reabsorbed into the

bloodstream where it is able have an effect on the body that is more prolonged than usual. A reduction in blood flow to the kidneys means that the amount blood containing serum albumin bound midazolam reaching the kidneys is significantly reduced which leads to increased levels of midazolam present in the body. These increased levels produce pharmacological effects on the body that are more profound than normal. Therefore, the decline in renal function in the elderly is closely related to the incidence of adverse drug reactions. All of the literature is in agreeance that the decline in kidney function and the reduction of its ability to filter blood with an increase in age are reasons that adverse drug events occur in elderly patients. The reduction in renal excretion simply causes the drug to stay in the body for longer than was normally intended.

Pharmacodynamic Changes -

Physiological changes that occur with aging also increase the pharmacodynamic response of the elderly patient. An increased pharmacodynamic response leads to increased drug sensitivity in the geriatric patient. These changes include alterations to receptors (i.e., receptor composition) and receptor affinity in the central nervous system. This means that the subunits of receptors change with aging that, therefore, change the affinity of receptors to anesthetics like midazolam. Most of the literature asserts that this is what mostly accounts for the elderly being affected by midazolam more than the younger population.

GABA neurotransmitter system alterations and aging -

Alterations to receptor numbers and affinity in the central nervous system are one of the main reasons for increased drug response to midazolam in the elderly patient. GABA is the primary inhibitory neurotransmitter in the brain, and it plays an important role in reducing neuronal excitability throughout the nervous system and in producing a calming effect on the

brain (31). Midazolam is metabolized by the gamma-aminobutyric acid (GABA) neurotransmitter system, and changes in the GABA neurotransmitter system increase the sensitivity of elderly patients to benzodiazepines such as midazolam. Essentially, midazolam's mechanism of action consists of the drug allosterically binding to the $GABA_A$ receptor of the GABA neurotransmitter system which alters the binding site of the receptor. Therefore, when GABA binds to the $GABA_A$ receptor, more ligand-gated chloride channels are opened than usual, which allows more chloride ions to enter the post-synaptic neuron. This increase of chloride ions entering the post-synaptic neuron then increases the inhibitory effect that the GABA neurotransmitter has on the body. As a result of changes in the GABA neurotransmitter system, elderly patients are more susceptible to the adverse effects of midazolam such as ataxia, sedation, and cognitive impairment (10).

This process leads to the anesthetic effect of midazolam because the increase of chloride ions entering the post-synaptic neurons causes inhibitory post-synaptic potenitals (IPSPs), which means that the post-synaptic neuron is less likely to fire an action potential and this is how neurons in the brain communicate. Therefore, a decrease in action potential firing causes less communication between neurons, and this is what leads to the pharmacological effects that midazolam has on the body.

The inhibitory actions of GABA are mediated by three receptor classes ($GABA_A$, $GABA_B$ and $GABA_{A-\rho}$). The $GABA_A$ receptor is involved in, and regulates, the majority of fast inhibitory neurotransmission in the brain, and as a result, is involved in drug response. The $GABA_A$ receptor contains an intrinsic ligand-gated chloride channel, formed by the assembly of many types of subunits, and at least twenty genes encoding distinct receptor subunits have been identified. These subunits are grouped according to their degree of sequence identity (α1–6, β1–

4, γ1–3, ρ1–3, δ, ε, π and θ subunits). The α1, α2, α5, β2, β3, and γ2 subunits are widely expressed in the human hippocampus, and the majority of $GABA_A$ receptors are comprised of two α subunits, two β subunits, and one γ subunit (Figure 4). The makeup of subunits of the $GABA_A$ receptor determines the type of benzodiazepine activity that is mediated. $GABA_A$ receptors containing the α1, β2/3 and γ2 subunits mediate sedative, anterograde amnestic and anticonvulsant actions, while receptors containing the subunits α2, β2/3, and γ2 mediate anxiolytic and muscle relaxation. Receptors containing α1, β2, and γ2 subunits are the most abundant subtype of the $GABA_A$ receptor in the brain, and these receptors comprise the major benzodiazepine binding sites (8).

Increased affinity of $GABA_A$ receptors to midazolam may be explained by the presence of the α1 subunit in the $GABA_A$ receptor complex, whereas lower affinity receptors appear to be composed of α2, α3, α5 subunits. This indicates that increases or decreases in the proportion of receptors containing a particular α subunit may likely reflect the affinity of the receptor for a specific benzodiazepine. Studies examining ion flux in membrane vesicles have revealed functional changes in $GABA_A$ receptors during aging. Age-related increases of α1-containing $GABA_A$ receptors and the increase of α1 binding density have been reported in the hippocampus. As a result, age-related pharmacological alterations in $GABA_A$ receptors do occur, which would produce a greater inhibitory effect. This means that the increase of α1 subunits on the $GABA_A$ receptor helps to boost receptor-drug affinity, and the more drug bound to receptors results in an increase in opened ligand-gated chloride ion channels, which intensifies the inhibitory effect of GABA. One study used midazolam as an example and stated that it is known to bind to α1 subunit containing $GABA_A$ receptors. This study then showed that midazolam is found to

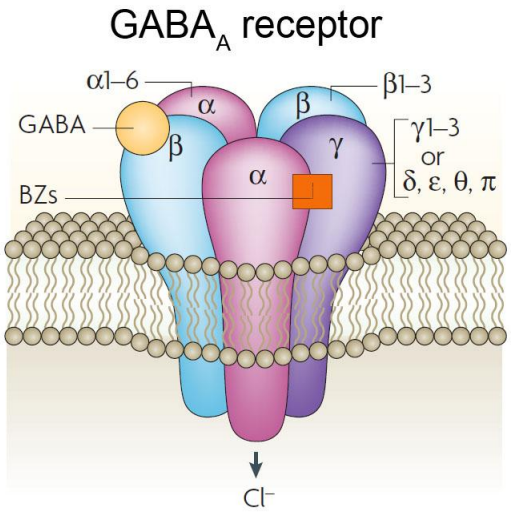
produce a greater potentiation of GABA-mediated currents in aged cells because of this increase in α1 subunits (31).

Another study found similar findings, and showed that age-related changes in the subunit expression of hippocampal $GABA_A$ receptors have been found. The research has revealed that α1 subunit messenger RNA expression was significantly increased in the hippocampus of old rats by 34%. The increased α1 messenger RNA and protein expression led to increased proportions of assembled $GABA_A$ receptors that contained α1 subunits (32). Therefore, the literature has stated that increased affinity of the $GABA_A$ receptor to midazolam and other benzodiazepines in the hippocampus is due to increased expression of the α1 subunit in the $GABA_A$ receptor (32).

A different study has proposed that the γ2 subunit of the $GABA_A$ receptor is important in the potentiation of GABA inhibition, and that increased expression of the γ2 subunit in the $GABA_A$ receptor increases the inhibitory effect of the GABA neurotransmission system (33). The γ2 subunit of $GABA_A$ receptors is highly expressed throughout the brain, and a knockout of γ2 results in about a 94% reduction of midazolam binding sites. Essentially, this study is stating that the $GABA_A$ receptor's affinity for midazolam is increased by the presence of γ2 subunits which leads to more chloride channels being opened, and an increase in age has resulted in the slightest subsequent increase of γ2 subunit in the $GABA_A$ receptor (33). Another study found that γ2 subunit expression increased slightly, by 7%, in the aging hippocampus, but that the increase in α1 subunit expression greatly dwarfed the increase of the γ2 subunit in the $GABA_A$ receptor (34). There are conflicting opinions on which subunit of the $GABA_A$ receptor helps to increase the inhibitory effects of the GABA neurotransmitter when benzodiazepines such as midazolam are bound to it in the aging patient, but a change in the subunit composition in geriatric patients appears to lead to increased responses to midazolam. Perhaps both subunits

play an important role in the increased inhibitory effects of GABA on the bodies of the elderly when compared to the younger population.

However, after reviewing the studies and the literature, it is my opinion that both an increase in the α1 and γ2 subunits help to potentiate the facilitating effects of midazolam on the GABA neurotransmitter. GABA binds to the $GABA_A$ between one of the α subunits and one of the β subunits and this is what is known as the binding site. It is well known that midazolam binds allosterically to the $GABA_A$ receptor, and midazolam actually binds to a site between one of the α subunits and the γ subunit (Figure 4). This shows that the opposing sides of the literature are both correct since changes in both subunits are helping to increase the affinity that the $GABA_A$ receptor has for midazolam and to subsequently increase the inhibitory effects of the GABA neurotransmitter. Both of these increases in the α1 and γ2 subunits are important to understanding why midazolam has such a profound effect on the elderly population since the allosteric binding site of midazolam is located between these two subunits.



Jacob et al., Nature Reviews Neuroscience, 2008 (38)

Figure 4. Diagram of $GABA_A$ Receptor and Benzodiazepine and GABA Binding Sites

Concluding Remarks:

The increase in pharmacokinetic and pharmacodynamic responses as a result of physiologic changes in the aging body are the reason why the elderly experience more profound effects to midazolam than younger patients. Changes in the body mass of the elderly prolong midazolam distribution while changes to liver and kidney makeup and function cause midazolam build up and the drug to spend more time in the body causing adverse effects. Decreased serum albumin levels in the blood of an elderly patient also increase the amount of midazolam that is available to exert its pharmacological effect on the body. Perhaps the most important physiologic change that occurs in the body is the change in the subunit makeup of the $GABA_A$ receptor which increases the receptor's affinity for midazolam and intensifies the inhibitory properties of the GABA neurotransmission system, and this is done through the increase of α1 and γ2 subunits since the midazolam binding site is located between these two subunits. Of all the changes that occur in the aging body, these five changes are the main reasons as to why midazolam affects the elderly in such a negative way. All of these changes are important to understanding why midazolam effects the elderly population in such a profound manner, and if these changes can be fully understood then it will be a step in the right direction to establishing a safer medical environment for elderly patients and possibly counteracting the adverse side effects, not just of midazolam, but of most drugs.

It is of utmost importance to solve the mysteries as to why these physiologic changes are occurring in the aging body to help shed light on why midazolam adversely effects the elderly much more than younger patients, and why antagonistic pharmacokinetic and pharmacodynamics responses in geriatric patients occur. If these physiologic mysteries can be fully resolved, then it can lead to safer medical and anesthetic practices when it comes to

midazolam and its use. These safer practices can then hopefully help elderly individuals maintain their confidence and independence and keep prolonged amnesia, hysteria, functional deterioration, and depression from occurring.

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