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Systematic Review

A real-world systematic review of the forensic implications regarding serum testing in compliance monitoring

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ABSTRACT

The purpose of this systematic review is to study the correlation between the daily dose of oral opioids/ intrathecal opioids and resultant serum levels in relation to established blood toxicity levels used forensically. Between April 2018 and October 2022, serum opioid test results of 1,583 patients were analyzed from our clinical private practice. A broad literature search was conducted with the key words, "Blood concentrations of opioids", which returned 7,993 results in PubMed. A smaller search was performed in PubMed with the key words, "cytochromes that metabolize opioids", which yielded 1,387 results. Additionally, a confidential Excel spreadsheet was created by the American Institute of Toxicology Laboratories in Denton, Texas and was provided to our clinical practice. Simple linear regression was performed in Excel to determine the correlation coefficient, R-squared value, for each prescribed opioid. The result was an unexpected weak correlation between the daily opioid dose and serum concentration. The most surprising finding is an "overlap" between measured serum levels of all opioid groups with the toxic range in Baselt. In conclusion, the endpoint of opioid prescribing should focus on maximizing activities of daily living and achievement of functional goals utilizing serum level analysis, tempered by Centers of Disease Control guidelines. Serum testing can suppress physician vulnerability created by patients dying, (who were taking prescribed opioids). Future research analyzing the concentration of oral opioids in the cerebrospinal fluid in comparison to the concentration of opioids in the cerebrospinal fluid in the same patient after intrathecal opioid monotherapy would be interesting.

Keywords: Centers of disease control, Intrathecal opioid therapy, Morphine milligram equivalent, Opioid toxicity, Serum opioid levels

INTRODUCTION

The prescribing of opioids significantly increased in the 1990's due to changing attitudes of physicians regarding the potential for addiction in the treatment of chronic pain.[1] A one-paragraph correspondence letter published in the New England Journal of Medicine in 1980 was inaccurately referenced, triggering a pharmacologic tidal wave.[2] The Centers for Disease Control and Prevention (CDC) were concerned in the continued increase of overdose deaths and introduced guidelines in 2016 regarding opioid prescribing that targeted primary care physicians. A discussion of opioid therapy (by any route) would not be complete unless compliance is addressed. In this arena, urine drug testing (UDT) has been the norm in identifying illicit or nonprescribed controlled substances. Unfortunately, UDT does not provide quantitative information regarding prescribed opioids. In addition, there is a trend to obtaining plasma (the liquid portion of blood) drug concentrations to aid in treatment (therapeutic drug monitoring). Serum testing seems to be a promising alternative modality for patients that are on either moderate or high-dose opioids.[3] An "as-prescribed" approach is essential for serum testing to accurately quantify opioid efficacy. This approach assumes all patients ingest opioids according to the maximum daily dose of the recommended schedule.[4] Serum testing can offer guidance on establishing the appropriate opioid

dose regimen for each chronic pain patient and objectively quantifying opioid tolerance. Higher doses of opioids are required for chronic pain patients who have developed tolerance. Consequently, chronic pain patients who are tolerant can lead nearly normal lives with opioid serum concentrations that are higher than the range that is considered "therapeutic" or "toxic" for an individual who is not on opioid therapy. Thus, it is necessary to establish a context in which the results are evaluated, creating a duality between clinical and forensic toxicology. We propose anti-mortem documentation of opioid exposure is critical in establishing individualized baseline opioid levels. Currently, in overdose death investigations, the cause of death is often wrongly attributed to "toxic" levels of opioids. Furthermore, physicians strictly adhere to morphine milligram equivalents (MME) guidelines to potentially avoid the scrutiny of post-mortem blood analysis. Interestingly, Deer et. al. proposed that serum concentrations may not correlate to MME.[5]

Based on the discussion regarding MME and serum levels, we conducted a real-world, single-center retrospective analysis to determine whether there is a correlation between serum levels and the doses prescribed for intrathecal, transdermal and oral opioids in our pain management practice (California Advanced Pain and Spine Specialists) or known as CAPSS located in Fresno, CA. If there is a correlation between serum level and dose, then MME may be confirmed as a reliable metric. On the other hand, if there is weak correlation, then serum levels should be utilized to optimize opioid prescribing in conjunction with MME. Moreover, this is an opportunity to investigate antemortem serum levels in relation to established postmortem toxic ranges of opioids.

METHODS

A real-world study was conducted, bypassing the strict exclusion criteria that a randomized control trial (RCT) in order to ensure internal validity. The advantage of a real-world study is that we could maintain a single-center, large patient sample size promoting the generalizability of our findings.

Literature search

A broad literature search was conducted with the keywords "blood concentrations of opioids", which returned 7,993 results in PubMed. In addition, a smaller search was performed in PubMed with the keywords "cytochromes that metabolize opioids" that yielded 1,387 results. This search included fast and slow metabolizers regarding genetic testing and the percentage of the U.S. population that is a fast or slow metabolizer for opioids (hypo-metabolizers/hyper-metabolizers). Furthermore, more searches were conducted in PubMed, Google Scholar and Scopus with the keywords "opioid toxicity and serum levels", "serum levels (opioids) and intrathecal therapy" and "serum opioid levels and prescribed opioids". In addition, a search was completed in those 3 databases along with the New England Journal of Medicine (NEJM) with the keywords "opioid deaths in the U.S. (epidemics)" and a filter was applied to examine information from the "last 2 years"; the filter was later expanded to include the "last 10 years".

Data collection and analysis

A confidential Excel spreadsheet was created by the American Institute of Toxicology (AIT) Laboratories located in Denton, TX and sent to our clinical practice that listed all the patients who had serum tests performed on specific dates of service that ranged from April 2018 to October 2022.

SynchroMed™ II pump

95% confidence, 50% of the pumps have a flow rate repeatability of +/- 0.27% between successive 1 ml dispensed volumes within a refill cycle MRI Triangle**.** Under specific conditions for 1.5 T and 3.0 T MRI scans. Refer to product labeling.

Drug preparation (Hartley medical)

The intrathecal drug preparation was provided by Hartley Medical, Long Beach, CA. Hartley Medical, a national leader in IT preparation compounds patient specific formulations within an ISO 6 clean room facility. This pharmacy employed procedures which exceed USP 797 and State Pharmacy Laws to ensure accuracy and purity of final solutions.

Serum testing

Confirmatory serum drug analyses were performed using ultra performance liquid chromatography electrospray ionization tandem mass spectrometry (UPLC-ESI-MS-MS). A Waters Acquity UPLC chromatography unit was coupled with a XEVO TQS triple quadrupole mass spectrometer (Waters Corp, Milford, MA, USA), the latter operated in ESI-positive ionization mode.

RESULTS

There are a total of 1583 patients in the clinical practice who were included in this study (The serum data points were collected from 2018 through 2022).

It was found that intrathecal fentanyl has a weak correlation between daily dose and serum concentration. The serum concentration range for transdermal fentanyl in fatal opioid overdose cases as reported by Baselt is 3.0-28 ng/ml and our range is specified in Figure 1. A comparison of these serum concentration ranges was performed and 24 patients (22.2%) were within the toxic range published by Baselt. Intrathecal hydromorphone also has a weak correlation between daily dose and serum concentration. The serum concentration range for oral

hydromorphone in fatal opioid overdose cases as reported by Baselt is 20-1200 ng/ml and our range is specified in Figure 2. A comparison of these serum concentration ranges was performed and 88 patients (65%) were within the toxic range published by Baselt. Intrathecal morphine has a weak correlation between the daily dose and serum concentration. The serum concentration range for oral morphine in fatal opioid overdose cases as reported by Baselt is 200-2300 ng/ml and our range is specified in Figure 3. A comparison of these serum concentration ranges was performed and 30 patients (15%) were within the toxic range published by Baselt.

Oral hydrocodone has a weak correlation between the daily dose and serum concentration. The serum concentration range for hydrocodone in fatal opioid overdose cases as reported by Baselt is 130-7000 ng/ml and our range is specified in Figure 4. A comparison of these serum concentration ranges was performed and 116 patients (17.8%) were within the toxic range published by Baselt. Oral morphine has a weak correlation between the daily dose and serum concentration. The serum concentration range for oral morphine in fatal opioid overdose cases as reported by Baselt is 200-2300 ng/ml and our range is specified in Figure 5. A comparison of these serum concentration ranges was performed and 101 patients (72%) were within the toxic range published by Baselt.

Oral methadone has a weak correlation between the daily dose and serum concentration. The serum concentration range for methadone in fatal opioid overdose cases as reported by Baselt is 400-1800 ng/ml and our range is specified in Figure 6. A comparison of these serum concentration ranges was performed and 38 patients (14%) were within the toxic range published by Baselt.

Oral oxycodone has a weak correlation between the daily dose and serum concentration. The serum concentration range for oxycodone in fatal opioid overdose cases as reported by Baselt is 100-8000 ng/ml and our range is specified in Figure 7. A comparison of these serum concentration ranges was performed and 85 patients (28%) were within the toxic range published by Baselt.

Oral tramadol has a weak correlation between the daily dose and serum concentration. The serum concentration range for tramadol in fatal opioid overdose cases as reported by Baselt is 1600-48000 ng/ml and our range is specified in Figure 9. A comparison of these serum concentration ranges was performed and 10 patients (8%) were within the toxic range published by Baselt. Oral hydromorphone has a weak correlation between the daily dose and serum concentration. The serum concentration range for oral hydromorphone in fatal opioid overdose cases as reported by Baselt is 20-1200 ng/ml and our range is specified in Figure 10. A comparison of these serum concentration ranges was performed and 27 patients (75%) were within the toxic range published by Baselt. Oral oxymorphone has a very weak correlation between the daily dose and serum concentration. The serum concentration range for oxymorphone in fatal opioid overdose cases as reported by Baselt is 20-550 ng/ml and our range is specified in Figure 11. A comparison of these serum concentration ranges was performed and 8 patients (88%) were within the toxic range published by Baselt.

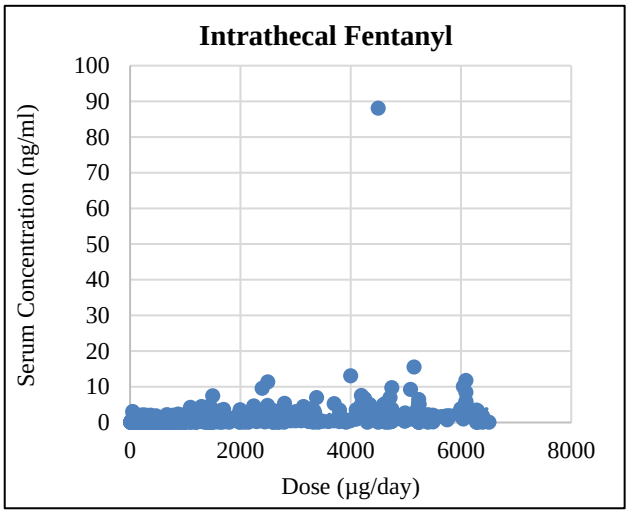

Figure 1: The correlation coefficient, R-squared, is 0.063. The mean daily dose is 1881.7 µg/day and the range is 15-6511 µg/day. The mean serum concentration is 1.25 ng/ml and the range is 0-88 ng/ml. The patient sample size for intrathecal fentanyl is 108 and the total number of data points is 614.

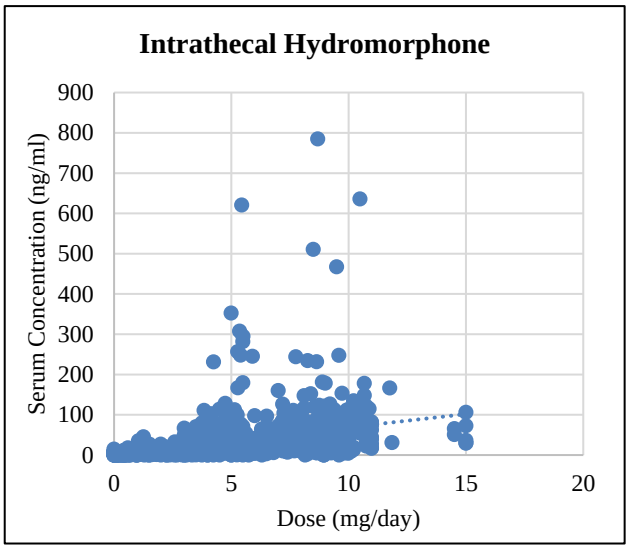

Figure 2: The correlation coefficient, R-squared, is 0.1231. The mean daily dose is 5.13 mg/day and the range is 1.27E-4 through 15.002 mg/day. The mean serum concentration is 36.9 ng/ml and the range is 0-784.9 ng/ml. The patient sample size for intrathecal hydromorphone is 135 and the total number of data points is 800. An unpaired, one-tailed t-test was performed to measure statistical significance between intrathecal and oral hydromorphone "p<0.001".

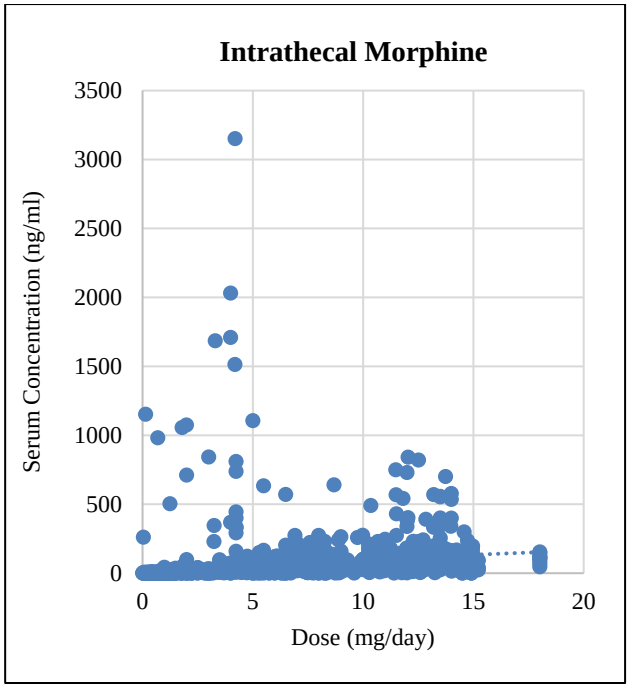

Figure 3: The correlation coefficient, R-squared, is 0.0251. The mean daily dose is 6.39 mg/day and the range is 8.01E-3 through 18.017 mg/day. The mean serum concentration is 78.8 ng/ml and the range is 0-3150.9 ng/ml. The patient sample size for intrathecal morphine is 199 and the total number of data points is 1014. An unpaired, one-tailed t-test was performed to measure statistical significance between intrathecal and oral morphine "p<0.001".

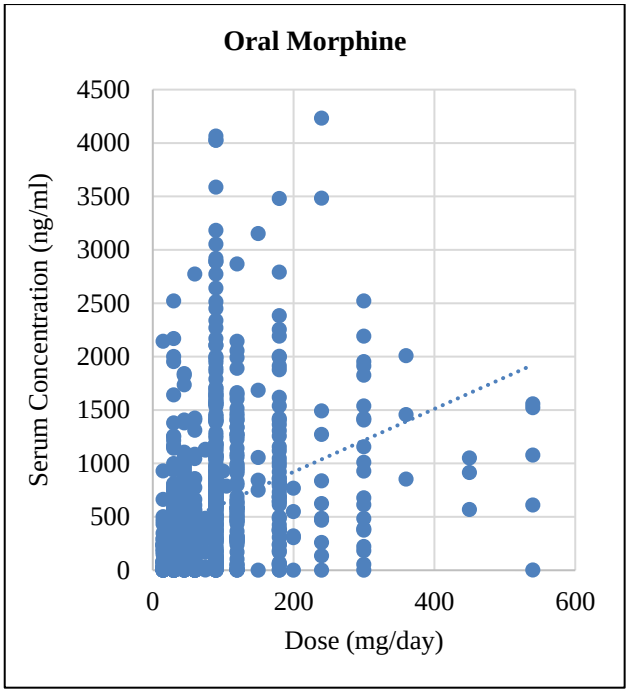

Figure 5: The correlation coefficient, R-squared, is 0.1019. The mean daily dose is 83.7 mg/day and the range is 15-540 mg/day. The mean serum concentration is 578 ng/ml and the range is 0-4232.2 ng/ml. The patient sample size for oral morphine is 141 and the total number of data points is 881. An unpaired, one-tailed t-test was performed to measure statistical significance between intrathecal and oral morphine "P<0.001".

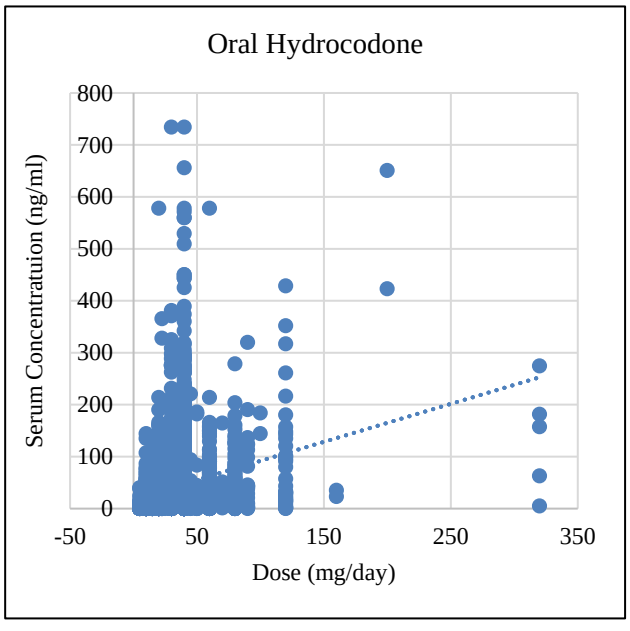

Figure 4: The correlation coefficient, R-squared, is 0.0533. The mean daily dose is 34.9 mg/day and the range is 5-320 mg/day. The mean serum concentration is 44.4 ng/ml and the range is 0-734.1 ng/ml. The patient sample size for oral hydrocodone is 652 and the total number of data points is 3794.

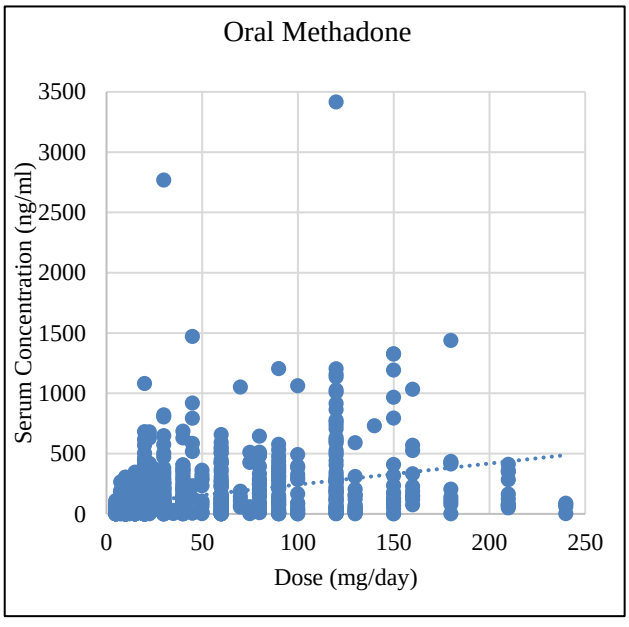

Figure 6: The correlation coefficient, R-squared, is 0.109. The mean daily dose is 37.8 mg/day and the range is 5-240 mg/day. The mean serum concentration is 134.7 ng/ml and the range is 0-3415.6 ng/ml. The patient sample size for oral methadone is 270 and the total number of data points is 1362.

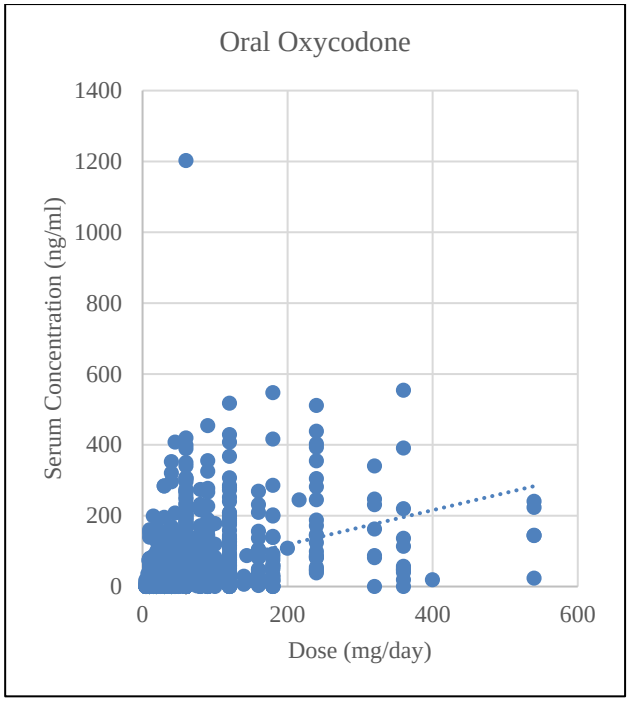

Figure 7: The correlation coefficient, R-squared, is 0.1321. The mean daily dose is 58.6 mg/day and the range is 5-540 mg/day. The mean serum concentration is 50.0 ng/ml and the range is 0-1202.07 ng/ml. The patient sample size for oral oxycodone is 301 and the total number of data points is 1608.

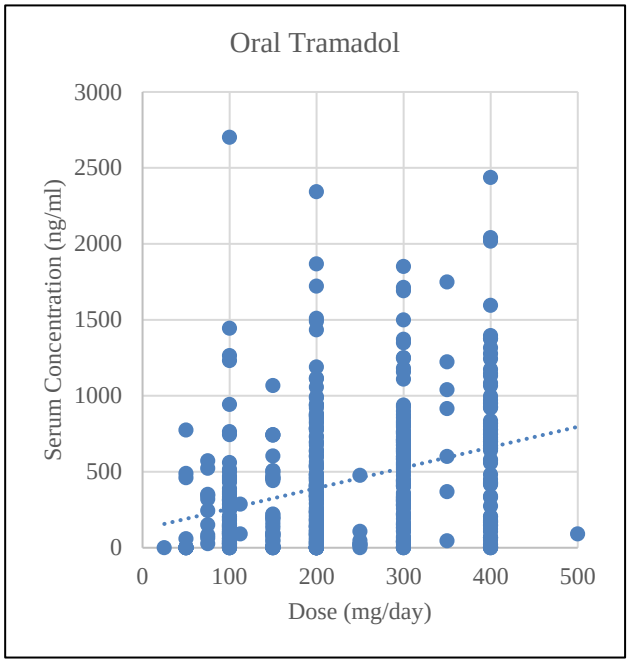

Figure 8: The correlation coefficient, R-squared, is 0.105. The mean daily dose is 225 mg/day and the range is 25-500 mg/day. The mean serum concentration is 426 ng/ml and the range is 0-2700.2 ng/ml. The patient sample size for oral tramadol is 120 and the total number of data points is 477.

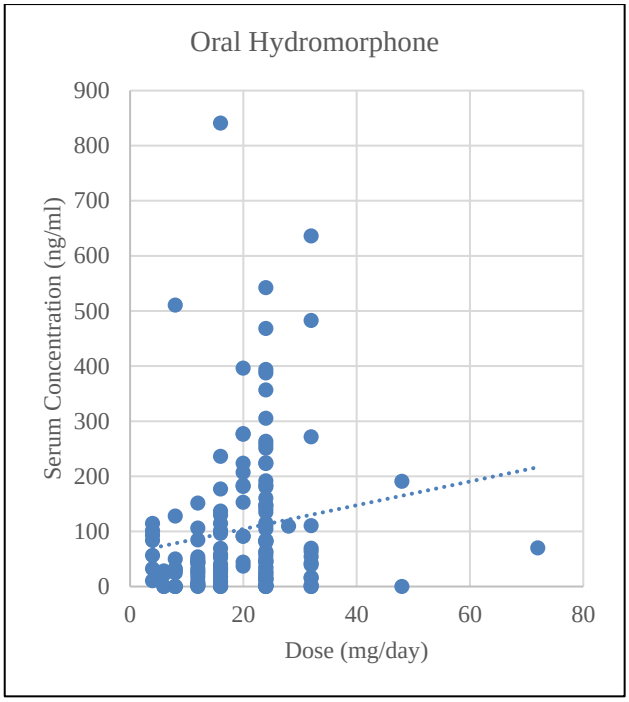

Figure 9: The correlation coefficient, R-squared, is 0.0219. The mean daily dose is 19.8 mg/day and the range is 4-72 mg/day. The mean serum concentration is 104 ng/ml and the range is 0-840.6 ng/ml. The patient sample size for oral hydromorphone is 36 and the total number of data points is 143. An unpaired, one-tailed t-test was performed to measure statistical significance between intrathecal and oral hydromorphone P<0.001".

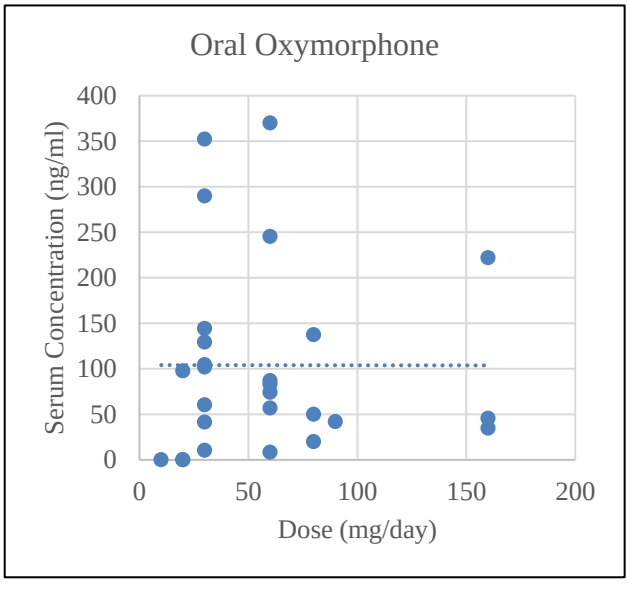

Figure 10: The correlation coefficient, R-squared, is 9E-07. The mean daily dose is 58.1 mg/day and the range is 10-160 mg/day. The mean serum concentration is 104 ng/ml and the range is 0-369.8 ng/ml. The patient sample size for oral oxymorphone is 9 and the total number of data points is 27.

DISCUSSION

In our study, there was an unexpected weak correlation between the daily opioid dose (oral, transdermal, intrathecal) and serum (the fluid remaining when blood has clotted) concentration. This has never been published and the implications are monumental. Accordingly, the clinical focus should not be linked to MME alone, but also on the utilization of a therapeutic drug monitoring approach. The CDC recommendations do not consider the increased requirements of opioid-tolerant patients. Prescribing to this population (a majority of chronic pain patients) should be judiciously optimized to ensure the continued maximization of function and activities of daily living (ADL) utilizing serum opioid levels and clinical vigilance. The concept of lowest effective dose (LED) should remain.

The most surprising finding in our study is the "overlap" between the measured serum levels of all opioid groups and the toxic range published in Baselt.[6] This begs the question: What are the ramifications of a blood sample drawn by the coroner in these patients? In forensic pharmacology, the question is usually "did a drug cause or contribute to the death?".[7] It has been shown that high plasma opioid concentrations reported in clinical studies are close to the concentrations in fatal opioid overdoses in opioid-tolerant cancer pain patients.[8] The interpretation of postmortem opioid data is challenging. Baselt's text, Disposition of Toxic Drugs and Chemical in Man, is referenced in forensic toxicology. A major limitation with case-specific references (Baselt) is the lack of consideration of confounding factors. These include underlying comorbidities, synergistic medication, drug tolerance and postmortem artifact. Thus, these references should not be utilized solely but, rather, as a starting point.[9]

In 2012, the National Association of Medical Examiners (NAME) and the American College of Medical Toxicology (ACMT) received financial support from the CDC specifically to address the certification of opioid drug related deaths (to include death investigation). The resultant position paper was updated in 2020. The panel recommends that an autopsy be performed by the medical examiner or coroner. Autopsies are the most accurate measure of determining the cause of death. Secondly, an inventory of medication was proposed to include state prescription drug monitoring programs. Thirdly, toxicological analysis was recommended in select situations.[10]

In this regard, blood is the ideal specimen for the quantification and interpretation of drug concentrations. Post-mortem analysis is performed on whole blood and antemortem samples are obtained from serum. Post-mortem samples of whole blood are generally obtained from femoral veins as this has the least likelihood of post-mortem changes.[7] Peripheral blood is less abundant than cardiac blood and blood samples are frequently obtained from that organ. However, blood levels in cardiac blood are generally higher than femoral samples. It is usually not feasible to separate red blood cells in postmortem blood and it is not surprising that its composition may differ from the blood of a living person.[11]

A significant issue with interpretation of post-mortem toxicology results is the "toxicological nightmare" of post-mortem drug redistribution. Postmortem distribution of drugs occurs along a concentration gradient from high concentration sites in solid organs into the blood. The lung is capillary rich and due to its high lipoproteins, contains the highest concentration of a drug in any organic structure in the body. Post-mortem diffusion from the lung and liver results in significant drug elevations in the inferior vena cava, pulmonary artery, pulmonary vein and eventually the heart. As a result, postmortem concentrations in blood are site-dependent for many drugs. This creates a major obstacle in the significance of post-mortem drug concentrations in blood. The premise that post-mortem drug concentrations parallel drug concentrations at the time of death is not valid. The occurrence of post-mortem drug redistribution weakens the database reference values in post-mortem blood where the sample site is unknown.[12]

In light of the previous discussion, a promising alternative to the utilization of oral opioids in the treatment of opioid-responsive pain is intrathecal therapy. In our study, the mean serum level of I.T. morphine was 78.8 ng/ml as compared to 578 ng/ml for oral morphine. Of interest, the mean serum level of I.T. morphine was higher than I.T. fentanyl (1.25 ng/ml). One would have expected the opposite finding based on an elegant pharmacokinetic study of spinal distribution and clearance which demonstrated a slower vascular uptake of I.T. morphine in contrast to I.T. fentanyl. This conclusion was based on transfer rate constants and not measured serum levels in pigs.[13] The I. T. morphine and I.T. hydromorphone had serum levels that were statistically.

Hydromorphone had serum levels that were statistically significantly lower than their oral counterparts. This can largely be explained by the blood brain barrier (BBB). Approximately 400 miles of capillaries traverse through the spinal cord and brain. Most organic structures are supplied by capillaries lined with porous endothelial cells permitting rapid movement of small molecules into the organ from the blood. However, the spinal cord and brain have endothelial cells that are sealed together with continuous tight junctions. As a result, the BBB drastically prevents almost all molecules from entry into the brain and spinal cord, the exception includes small lipophilic molecules and those where active transport is involved. This finding explains the requirement of large doses of oral opioids to achieve adequate analgesia (opioid receptors are in the spinal cord).

The first study that measured serum opioid levels and clinical outcomes in cancer patients treated with intrathecal opioids was conducted by Brogan et al. This

was a prospective observational study in 51 cancer pain patients who ranged in age from 18 to 90 years. Intrathecal therapy was performed with the Medtronic SynchroMed II pump (Minneapolis, MN). 87.5% of these patients ceased taking non-IT opioids and 53% had undetectable serum opioid concentrations (less than 2 ng/ml) at the 4-weeks mark. 92% were not ingesting non-IT opioids and 59% had undetectable serum levels at the 8-week mark. IT morphine doses less than 4.2 mg/day were not detectable, whereas IT hydromorphone doses less than 6.8 mg/day were not detectable.

Interestingly, at 4 and 8 weeks, there was no difference in the level of pain in patients with undetectable serum levels versus those who had detectable serum levels. Moreover, there was a major reduction in serum opioid concentrations when IT therapy was utilized to treat cancer pain.[14] In our study, the minimum detection limit (cutoff) was 0.1 ng/ml for all analytes. We did not encounter a single intrathecal data point that was nondetectable. Brogan's cutoff for all analytes except fentanyl was 2 ng/ml. This may account for his undetectable serum levels. Also, Brogan did not address the correlation of daily delivered dose and resultant serum levels.

There was another study conducted in a single medical practice (similar to our pain management practice) that assessed patient satisfaction regarding intrathecal opioid therapy provided by the Medtronic SynchroMed II pump (Minneapolis, MN) for benign chronic pain. In this study, there were 610 patients who were receiving targeted drug delivery (TDD) who were sent an 18-question survey and 443 of these patients completed this survey.

The survey measured three metrics including improvement of quality of life, improvement in physical function and pain relief. Ninety-four percent of these patients had improved pain control after pump implantation. In addition, 77.6% reported that they experienced enhanced physical functioning and 86.4% indicated that they had improved quality of life following pump implantation. Lastly, 38.9% of patients said they solely depended on TDD for pain control.[15] In our study, 56% of TTD patients did not require additional oral opioids.

Despite the significant benefit of a real-world study for our research, there could be misclassification of data due to a discrepancy between the opioid dose recorded in the EMR and the actual dose patients are taking for their chronic pain treatment. In addition, patients may have recall bias emphasizing impactful events that could affect the type of opioid therapy they receive from our clinical practice.

CONCLUSION

This study emphasizes the following points. First, the endpoint of opioid prescribing should focus on maximizing activities of daily living and achievement of functional goals utilizing serum level analysis. Second, serum testing can suppress physician vulnerability created by patients dying who were taking prescribed opioids. Third, serum testing is superior to urine testing in compliance monitoring due to its quantitative nature. Fourth, a drug can be the cause of death at a concentration below the toxic range. On the other hand, a drug concentration in the toxic range does not necessarily make it the cause of death. Fifth, tolerance may be responsible for the overlap between therapeutic serum levels and published toxic levels (there is no quantifiable reliable determination of opioid tolerance prior to or after death).

Sixth, intrathecal opioid trials should be considered in the determination of opioid responsivity in patients who insist on repeated oral opioid rotation. Lastly, intrathecal therapy should be considered in the treatment of chronic opioid-responsive pain refractory to oral opioids and, in opioid use disorders. Future research analyzing the concentration of oral opioids in the CSF in comparison to the concentration of opioids in the CSF in the same patient after intrathecal opioid monotherapy would be interesting. In addition, should the endpoint of intrathecal opioid titration reflect the intrathecal concentration measured when oral opioid monotherapy was utilized?

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