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SPECIAL ARTICLE

From the *Journal* archives: Apparatus for demand analgesia with parenteral opioids: from leading role to supporting cast

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Editors' Note: Classics Revisited

Key Articles from the *Canadian Journal of Anesthesia* Archives: 1954-2013

As part of the *Journal's* 60th anniversary Diamond Jubilee Celebration, a number of seminal articles from the *Journal* archives are highlighted in the *Journal's* 61st printed volume and online at: www.springer.com/12630. The following article was selected on the basis of its novelty at the time of publication, its scientific merit, and its overall importance to clinical practice: *Keeri-Szanto M*. Apparatus for demand analgesia. Can Anaesth Soc J 1971 18: 581-2. In this article Dr. John Penning presents expert commentary on a prototype patient-controlled analgesia apparatus described by Dr. Keeri-Szanto in the legacy Canadian Anaesthetists' Society Journal, published in 1971. The prototype utilized a compact, relatively inexpensive syringe driven motor mechanism - a system that could be employed with safety, for the first time, on surgical wards.

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Recent medical school graduates belonging to the "smartphone" generation seem hardly impressed by opioid delivery via intravenous patient-controlled analgesia (PCA). Programmable PCA pumps are now widely used in Canada for control of acute postoperative pain. Since the advent of newer modalities, this "workhorse" of the acute pain service (APS) seems to have lost most of its "wow" factor and certainly seems taken for granted. Nevertheless, its advent on the scene of perioperative pain management was a remarkable advance. Together with neuraxial opioids, it helped usher in the creation and early development of anesthesiology-directed APS around the world.[1] The landscape of perioperative pain management was to be changed forever.

Before PCA, the principal means of parenteral opioid delivery was intermittent intramuscular or subcutaneous injection on a q3-4h "as needed" basis. This approach had two major limitations. First, usually a very limited range in dosage options was offered. Even in opioid naïve patients, a fivefold patient to patient variability has been shown in the minimum effective serum concentration of fentanyl (0.23-1.18 $ng \cdot mL^{-1}$) for adequate postoperative pain control.[2] Added to this is the variability in absorption from the site of opioid injection to serum. All this makes the goal of attaining an effective serum level for the individual patient a "stab in the dark". Patient-controlled analgesia permits a much greater range in opioid dose available to the patient. The second major limitation of nurse-administered parenteral opioids is the implication for nursing workload. Outside critical care areas, the patient to nurse ratios cannot support immediate on patient demand parenteral opioid administration. Hence, administration intervals are spaced at least three or four hours apart, and patients' serum opioid levels can oscillate from too low to too high and are rarely "just right". Patient-controlled analgesia permits the patient to self-administer smaller boluses more frequently, allowing the patient to spend much more time with a serum drug level in the desired effective analgesia zone while avoiding the higher serum

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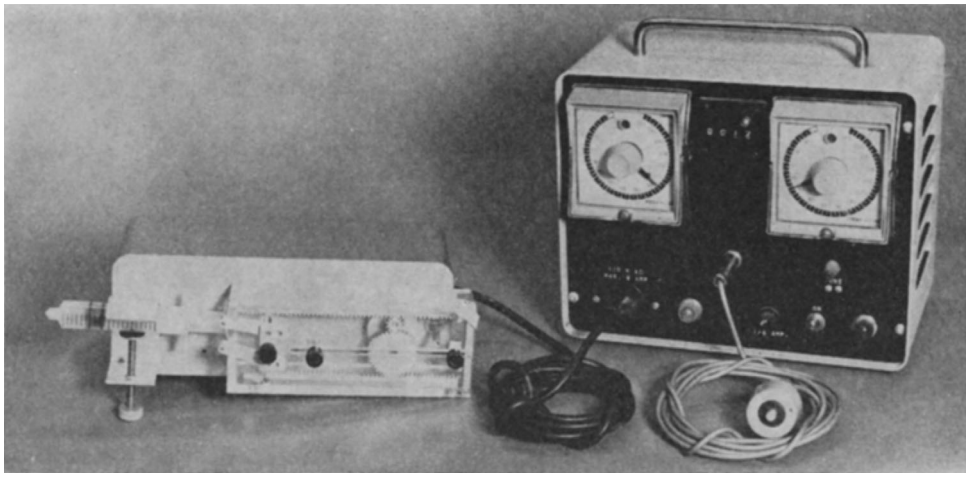

Figure The complete apparatus. Left: The motor syringe. Right: The switchbox. Top array, lft to rt.: Timer A, counter, timer z. The dark circles at 12 o'clock on timer dials are pilot lights. Middle array, 1/t. to rt.: push-button lead, beeper light. Bottom array, lft. to ft.: motor syringe socket, motor syringe circuit pilot light, fuse, on-off switch, switch-box circuit pilot light. Wiring diagram may be obtained by applying to the manufacturer-Canadian Algor Ltd, 159 Albert Street, London, Canada. Reproduced with permission from: *Keeri-Szanto M*. Apparatus for demand analgesia. Can Anaesth Soc J 1971; 18: 581-2

levels that produce side effects. An added advantage of PCA is the psychological benefit the patient derives from the sense of control over their pain.

The short technical paper by Keeri-Szanto is notable because it presents a novel description of a PCA device used in Canada.[3] The device was introduced in the late 1960s at Victoria Hospital, University of Western Ontario in London, Ontario. The author references several key articles published in the American literature that had already laid the groundwork in several key aspects. Scott emphasized the concept and merits of patient-controlled analgesic administration, first popularized with the use of nitrous oxide-oxygen for labour and delivery in the 1930s.[4] Scott's apparatus was exceedingly simple, allowing the patient to open a spring-loaded clamp for analgesic flow to occur from a secondary intravenous bag containing a limited "safe" dosage. A paper by Sechzer[5] describes the important fail-safe feature that we now refer to as the "lock-out interval". In a short technical paper, Forrest[6] also describes the lock-out interval and, furthermore, introduces the concept of a maximum dose limit per given time interval. The device had an additional safety feature, i.e., to default to a closed position in the event of a power failure. The PCA devices by Sechzer and Forrest advanced to a hand-held button used to activate a PCA pump. These pumps could deliver an individualized dose set for a specific patient, but they still used a secondary intravenous line from a separate intravenous bag containing the analgesic. The technology at the time was bulky, expensive, and time resource heavy. Consequently, the devices were unsuitable for day-to-day use on the surgical wards. Keeri-Szanto made a significant step forward in simplifying the apparatus by incorporating a syringe driver in his PCA device that would connect into the side port of the patient's intravenous line. The author concedes that it is inherently hazardous to have a potentially lethal dose of opioid hooked up to the patient; however, various fail-safe features inherent in the device assured that large single boluses were unlikely to occur. The disposable plastic syringe was driven by a motor so no gravity feed was involved. The machine would stop in the event of a power failure, and the driving power chosen for the motor syringe was low enough that it would stall in the event of an obstruction in the intravenous line. This would prevent infusing the analgesic upstream into the main line's intravenous bottle—this was in an era before one-way (anti-reflux) valves were standard in most intravenous infusion sets. While the device did have a secondary circuit that immobilized the syringe driver for a selected time period after bolus delivery was completed, i.e. a lock-out interval, it is interesting that this was not listed in the article as one of the key fail-safe features. The device offered a choice of from one to 30 min for the lock-out interval (Figure).

In the early days of intravenous PCA implementation, it was hoped that better postoperative analgesia afforded by this new device would translate into better patient outcomes and shortened length of hospital stay. Pain control and patient satisfaction are improved when compared with intermittent "on-demand" parenteral opioids. Nevertheless, intravenous PCA alone, even when managed by an APS, does not appear to yield improved outcomes in morbidity, mortality, and length of hospital stay.[7-9] Also, the incidence of opioid-related side effects

are similar with intravenous PCA compared with the traditional parenteral routes.[10] It is more difficult to define how serious complications such as anoxic brain damage and death compare because the incidence is so low and reporting is not always reliable. Even so, there is no doubt that there have been device-related patient casualties along the road of PCA device development. These devices were introduced in an era when system safety engineering and care and attention to the human-device interface were not as widely developed as they are today. A clear case in point was published in the Canadian literature, specifically, in the *Journal* in 2003.[11] Vincente *et al.* described a case of morphine overdose causing death in a young patient after Cesarean delivery. The PCA pump had been programmed for morphine 1 $mg \cdot mL^{-1}$, a 2-mg bolus dose, and a four-hour dose limit of 30 mg. Nevertheless, instead of the usual syringe containing morphine at 1 $mg \cdot mL^{-1}$, a morphine syringe containing 5 $mg \cdot mL^{-1}$ had been loaded into the PCA pump. This led to the administration of PCA boluses of 10 mg and effectively a four-hour dose limit of 150 mg. The patient was found vital signs absent about nine hours after delivery; 23 of the 30-mL morphine syringe had been infused (115 mg) despite the pump reading only 23 mg. The authors conducted an exhaustive search of the U.S. Food and Drug Administration Medical Device Reporting database and of the published literature (as of July 2000) for deaths attributed to user error with this particular PCA pump and found at least five similar cases. The strikingly important finding was that all reported deaths with this particular device were due to the pump programmer inadvertently entering a drug concentration that was much lower than that in the drug syringe. This is now a well-recognized hazard with all medication infusion pumps. It is clear that the lock-out interval and hourly dose limits alone are not adequate protection to prevent opioid overdose. There needs to be proper patient selection and standardized PCA orders, and appropriate education for patients, families, and nurses must be provided. The risk of "PCA by proxy" is particularly hazardous, i.e., where someone other than the patient decides when the PCA device is activated. There should be rigorous requirements for patient monitoring and re-assessment of PCA parameters. Also, drug options should be limited to as few as possible with equipotent concentrations between opioid syringe choices. Nevertheless, try as we might, human error will at times still prevail. It is incumbent upon us to minimize this potential for human error and eliminate the risk wherever possible. With the use of modern engineering technology, i.e., the use of "smart pumps", the potential for administering the wrong drug, at the wrong concentration, in the wrong patient, by the wrong pump, via the wrong route should be virtually 100% avoidable.

Before considering safety aspects regarding the pump itself, the opioid delivery system must be protected against the possibility of gravity-driven free-flow of the opioid solution. This is best achieved by using tubing for PCA opioid delivery that has a built-in anti-siphon valve. An anti-siphon valve looks like a typical one-way valve but requires a far greater driving pressure to open the valve (usually a minimum of 100 cm H_2O). This will prevent free-flow of drug if the pump driving mechanism should ever become disengaged from the drug solution syringe/bag or if the syringe should ever become cracked or punctured.

Another potential hazard may occur when an occlusion close to the intravenous site causes retrograde flow of opioid solution up the patient's main intravenous line or up an added secondary line. In this circumstance, the patient would be at risk of receiving a large opioid bolus once the occlusion is rectified. The patient's main intravenous line and any secondary added lines should all have one-way valve protection in order to prevent retrograde flow of the opioid solution.

The most important new safety feature available on PCA pumps is the menu-driven drug library and presets for PCA parameters. As previously stated, the most hazardous mistake that has likely been the cause of more lethal errors than any other intravenous PCA issue is the incorrect programming of the drug concentration. Unfortunately, the magnitude of the error is most often at least tenfold, e.g., when the concentration is entered as 0.1 $mg \cdot mL^{-1}$ for a 1 $mg \cdot mL^{-1}$ drug. An even worse error occurs when $\mu g \cdot mL^{-1}$ is chosen for a drug whose concentration is $mg \cdot mL^{-1}$. The "smart" PCA pump prevents these issues as follows: When the pump is turned on, the operator picks the modality from the menu. When intravenous PCA is chosen, in the next screen, the operator chooses either the standard first-line drug option or other secondary drug options. All drug options in the menu have standardized concentrations so no entry of concentration is required. The operator needs only to choose the drug at the pre-set concentration. Secondary drug options should be few and only for specific purposes. Once a drug option is chosen, the next menu screen provides the pre-set PCA parameters, such as bolus size, lock-out, continuous infusion, and hourly limits. Naturally, PCA is not a one-size-fits-all modality. When the standard pre-set parameter is not suitable, adjustments are permitted, but the "smart" pump has soft limits that, if exceeded, will warn the operator that the chosen setting is out of the commonly anticipated range for the medication chosen. Also, the pump has hard limits beyond which the parameters cannot be adjusted without a special program code available to a few specialists. These features are now available on all the leading PCA pumps available in Canada.

Menu-driven drug libraries help prevent the problem of wrong drug concentration and wrong PCA parameter settings but do not prevent wrong drug, wrong patient, and wrong route. Try as we might, even independent double checks are not 100% reliable. The solution is a "smart" pump with barcode medication administration (BCMA). The PCA prescription is scanned and the identification of the patient, the medication, and the PCA pump settings are verified. This technology is only recently available for a limited number of pumps; yet, no doubt in the near future, we will see wireless technology that is able to integrate computerized prescriber order entry, BCMA, and electronic medication administration record systems. Thinking ahead, there is the possibility of PCA pumps wirelessly paging the nurse when the patient's PCA use increases significantly or the PCA demand: PCA delivered ratio exceeds a specified ratio.

Today, where does the intravenous PCA modality fit into the context of multimodal analgesia? For centuries, opioids have been considered the cornerstone and principal therapeutic arsenal against severe postoperative pain. Until recently, the PCA pump has served as the "flag-ship" of the APS, front and centre on the stage of modern pain control. Nevertheless, times are changing. It is not good enough for our patients just to be comfortable in bed; we want our patients to feed and ambulate as quickly as possible. That is the key to better patient outcomes and savings in hospital costs. We aim for good pain control, but we also need freedom from the burden of opioid side effects. Appreciation of the phenomenon of opioid-induced hyperalgesia is a second reason to avoid aggressive opioid therapy.[12,13] The third and increasingly alarming reason for considering the use of opioid-sparing strategies is to decrease the load of opioids that we physicians are sending out into our communities. Abuse of medically prescribed opioids is reaching epidemic proportions. It is a bigger issue than the illicit use of cocaine or heroin. The use of non-medical prescription opioids likely now constitutes the third highest level burden of disease from substance abuse (after alcohol and tobacco).[14] Also, there are personal and societal costs associated with the criminal activity related to opioid abuse.

Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), formerly referred to as opioid adjuncts, now play the foundational role, the first to be started and, in most cases, the last to be discontinued. The new featured players are drugs such as coxibs, gabapentinoids, ketamine, intravenous lidocaine, and multimechanism weaker opioid analgesics like tramadol and tapentadol with markedly less potential for abuse. There will be a role for intravenous PCA opioids for many years to come, but in most cases, we should consider it as the supporting role, the top of the analgesic ladder used to supplement multimodal analgesics. Thereby, ideally the potent opioids may be used at the lowest dose required and for the shortest period of time possible.

The Keeri-Szanto article was a short descriptive technical article without presentation of any clinical patient data; however, it truly marked a pivotal point in time by illustrating how the intravenous PCA modality could be deployed safely to the surgical wards with the use of motor syringe technology and fail-safe mechanisms and led to the much wider application of this new modality. Nevertheless, even back then, the author put forward a "clinical pearl" that even today is sometimes not appreciated. He states, "Demand analgesia is at its most advantageous when the patient triggers the machine no more than two or three times per hour." This wise assertion is frequently not appreciated, especially with regard to managing the opioid-tolerant patient. A PCA bolus of 1 mg of morphine with a six-minute lock-out does not work ideally for all patients requiring anywhere from 0-10 $mg \cdot hr^{-1}$ To quote Dr. P.E. Macintyre, "PCA is not a "one size fits all" or a "set and forget" therapy and original prescriptions may need to be adjusted if maximal benefit is to be given to all patients."[15]

Key points

- The PCA apparatus described by Keeri-Szanto utilized a compact relatively inexpensive syringe driver motor mechanism, a system that could be employed on surgical wards. *Apparatus for demand analgesia* was published in the *Journal* in 1971, and it took another 20 years before the technology became widely popularized throughout Canada.
- The intravenous PCA pump has made a revolutionary impact on postoperative pain management. Together with the modality of neuraxial opioids, PCA was instrumental in ushering in the creation and early development of the anesthesiology-directed APS.
- The major advantage of PCA is the capacity to provide the patient with an individualized dosage of opioid on demand while saving on nursing labour requirements.
- The safety parameters, such as the lock-out interval and the hourly limit, do not provide complete safety against the possibility of opioid overdose. Menu-driven pumps should be used to avoid very dangerous programming errors such as improper drug concentration. Bar code reading technology, now available on a limited number of pumps, will provide additional safety.
- The PCA pump helps in managing postoperative pain in the opioid-tolerant patient. Patient-controlled parameters need to be adjusted so that analgesia may be maintained with three or fewer boluses per hour.

- The role of intravenous PCA opioids is changing as the cost of the burden of opioid side effects is appreciated. In the context of multimodal analgesia, intravenous PCA opioids may be used to supplement foundational analgesics such as acetaminophen, NSAIDs, and weaker opioids such as tramadol.

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