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# **EDITORIAL**

## **A plea for an independent holistic anaesthesia delivery system**

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When addressing an urgent plea as is presented here, firstly one has to explain what is an independent holistic anaesthesia delivery system (IHADS), and secondary why there is such a need for it.

To get started, here comes the description of the IHADS, which is not yet an existing term but the most concise summarizing denomination that I can imagine. An IHADS is a computerized drug delivery system that controls actuators which in turn may be all kinds of anesthetic drug delivery units such as syringe pumps, vaporizers, injectors etc. All delivered anesthetic drugs (and here I emphasize that this comprises hypnotics, sedatives, tranquilizers, analgesics and supplemental medication, but not muscle relaxants) have to be incorporated into the system. At the core of the “system” is a central computer that contains the pharmacokinetic profiles of all these drugs and is able to calculate in real time their individual plasma and target concentrations plus their mutual interactions. The term “holistic” stands for “all-encompassing”, and therefore a holistic drug delivery system would simultaneously control and monitor the application of all involved anaesthetic drugs, which act at the same time in a patient. Instead of what we do now, namely having separately running state-of-the-art computerized infusion pumps, which have to be individually controlled, an IHADS would consist of a central processor (computer) unit, that communicates with several drug delivery units (e.g. infusion pumps, vaporizers) (Fig. 1).

Insert Fig. 1 here

By working in the frame of such a holistic anesthesia system, the infusion pumps are actuators only, in cybernetics called “slaves”. Such a system would be indeed holistic if it is able to deal with all kinds of anesthetic drugs that have either a sedative/hypnotic and/or an analgesic effect, independently of their route of administration. Therefore the system should be able to deal with all intravenous anaesthetics, as well as all inhalative agents. The basis of the calculations is the pharmacokinetic profile of the involved drugs as well as knowledge of their mutual interaction. The most advanced existing system of this kind is the Draeger SmartPilot® View [1]. However, this system is implemented in a Draeger own anaesthesia architecture and cannot be viewed as independent. Some additional limitations of this existing system are discussed further down.

In a first instant, the system must know which drug is delivered at which dosage or rate. This data input can be provided by 3 different ways:

1. Direct control of injection pumps which are part or are connected to the system. This would be the main feature of the device: a group of injection pumps which are controlled by a central computer. The pumps must not have an inbuilt processor; they only should report to the steering unit the inserted syringe type/size, eventual rise of resistance in the infusion system and the position of the plunger.
2. Manual input of drugs directly delivered by the user, eventually by choosing from a dropdown menu or by entering data via a keyboard. This would be suitable for drugs that have been given as boluses directly by the user. However, it would be preferable to avoid manual

interference and to apply even small volume bolus doses by electronically controlled syringe pumps.

3. Transferred data from external delivery units such as vaporizers or resulting drug levels from analyzers such as end-expiratory volatile agent concentrations.

The resulting plasma- and effect-site levels of all involved drugs should be calculated and monitored over time and displayed in a manner that their interaction is comprehensively visible to the user. Thus the core part of the system, which is a computer bestowed with a suitable software, represents both, the display of the ongoing pharmacological process, as well as the interface with which at least certain parts of the drug delivery (in particular the injection pumps) can be controlled and manipulated. It is self-understanding that the system initially needs to be informed about all characteristics of the patient that are relevant to perform the pharmacokinetic calculations. In an advanced system, these data might be automatically retrieved via a network connection from the patient data management system (PDMS) of the hospital. In an ideal configuration, the system is always informed about the actually running dosage systems and the history of each drug delivery. Additionally, it is also able to display the future plasma- and effect-site drug level courses, as they would develop if the actual dosage remains unchanged [2, 3].

As being a computer based drug delivery system, it would be rather easy to update existing software with improved or augmented data, to add new drugs and to modify existing algorithms according changes in the knowledge about their properties. Such a system is also expandable to acquire inputs from various monitoring devices and to generate output orders to various drug delivery systems. In any case, an IHADS would be very flexible and could be operated over a long period of time, even though the technical environment might change by time. For example, existing or future input from anaesthesia depth or analgesia intensity measurement devices could also be implemented into the display of anaesthetic activity.

The control of delivery and effect of neuromuscular relaxation is at this early stage not as urgent as the hypnotic/analgesic medication, but in a later stage a separate “channel” could be assigned to control the level of neuromuscular blockade as well.

As soon as such a system would be available in clinical practice, one also could include a partial or total closed loop control of drug delivery, as soon as precise and reliable monitoring of the underlying measurements is available in real-time. However, the recently available monitoring of the depth of hypnosis and even more so the intensity of analgesia are still not reliable enough to leave these inputs alone to supervise and to modify the drug dosages. Therefore, I don't advocate yet closed loop configurations and still suggest to leave the anaesthetist in charge to decide which pattern of hypnosis/analgesia interaction he chooses to be administered.

A user-friendly display of the actually running drug dosages would encompass at least 2 essential windows (Fig. 2).

Insert Fig. 2 here

One would be the a dynamic chart indicating the 3 relevant drug levels (e.g. the 1. target, 2. plasma and 3. effect site levels) as well as the flow generated by the delivery unit (e.g. pump infusion rate or vapor concentration setting) over time. This kind of display is very similar to that one implemented in the minuscule monitors of actual infusion pumps or better in the quite popular pharmacokinetic software "TIVAtainer" [4]. These multiple courses of simultaneously running drugs are arranged above each other, so that they all have the same time frame in the horizontal axis (that can be stretched or compressed according to the user's needs). The actual time is indicated by a vertical line running through all courses, which divides them into the "past" left of the line, and "future" right of the line. The "future" – which should appear in somewhat paler colors - naturally, contains the courses as they would run if the actual dosage remains unchanged. The course of the main hypnotic agent should also contain a color coded segment of dosages that show the resulting interaction zone caused by the concomitant additionally delivered analgesic drugs, as it is implemented in the "TIVAtainer".

The second half of the screen should be dedicated to a display that I would call "hypnosis-analgesia interaction matrix" (in short "matrix"), which is a two-dimensional coordinate system with the x-axis indicating the total hypnotic effect (of all active hypnotic drugs) and the y-axis indicating the total analgesic effect (of all active analgesic drugs). The fact that hypnotics and analgesics interact with each other, respectively that on a wide range the one drug quality can be replaced by the other, is well known. By increasing the analgesic component, one can reduce the hypnotic one and vice versa, without changing much in the overall "anesthesia depths" as is conceived more or less intuitively. But very few anesthetists really have a clear knowledge where in the large spectrum of this hypnotic/analgesic spectrum of interactions their actual anaesthesia is and in which direction it heads. Nevertheless, a growing concern for this circumstance can be seen in studies where a closer view on this interaction is presented [5].

The dimension and the units of the 2 axis have yet to be determined, for example by using appropriate surrogate parameter. In the case of the overall analgesic effect this can be represented for example by morphine or better remifentanyl equivalents (expressed in  $\mu\text{g/ml}$  effect site concentration), for the overall sedative-hypnotic effect one might employ propofol equivalents (also expressed in  $\mu\text{g/ml}$  effect site concentration). Important is, that all relevant drug effects are summarized in these two dimensions. When drugs with both properties such as ketamine are given, their hypnotic and analgesic component should be proportionally adjudicated respectively. Within the surface between the 2 axes, a flashy point is indicating the actual position of the "holistic" anaesthetic activity. The left low corner at the intersection of the 2 axis at the level zero indicates a completely awake state of the patient that also has no analgesic medication. Increasing sedative/hypnotic drug activity moves the point upwards in the matrix while increasing analgesic drug activity drags the point to the right. As a consequence, a point position far up and to the right shows a deep combined hypnotic/analgesic state, which is characteristic for a profound anaesthesia, while all possible other hypnosis/analgesia combinations would be instantly visible by recognizing the location of the point. A dotted curve in the

matrix delineates the probable threshold to respiratory depression, from which one would expect apnea if the flashy point is right and above it. To implement a “historical” 3<sup>rd</sup> dimension to this matrix, the path that has been passed by the point in a certain period might be displayed as a track on this surface. This track might fade by going back on time or might show a color change according to the time that has passed. If a change in dosage has been made, an arrow emerging from the flashy point indicates its impending move pointing towards the new location. The speed of the change can be coded in the size or color intensity of that arrow as well. Within the surface of the matrix, one could include spots that identify zones for certain surgical interventions that usually need a typical combination of hypnotic and analgesic activity. Another very useful feature of this matrix would be if it could be used as a 2 way interface between user and drug delivery. One way is to show the matrix-position as a result of the actual drug actions, the other one would be to enable the user to point on a new position for the flashy point on the matrix where to he would like to change its position (e.g. by clicking there with the computer mouse). This move induces respective output changes in the delivery units, resulting in modifications of the drug dosages till the flashy point arrives at the desired new position. The speed and dynamics of the dosage change should also be variably set by the user.

The question is whether such a system is really necessary, and since this manuscript is intended to be a “plea” it’s clear that in my opinion it is so. Not only the fact that all necessary components for an IHADS are already a rather long time available and it’s curious that they haven’t yet been assembled in this way already a long time ago. As a natural development in general technology, as soon as the theoretical and technological prerequisites for a novelty become available and are recognized as such, it’s only a matter of time till a new invention or development appears on the scenery. Our recent understanding for the combination of hypnotic and analgesic drug activity has been augmented considerably since potent and well steerable agents of both kinds are available (in particular propofol and remifentanyl). In addition, the mutual interaction of these drugs in the frame of a general anaesthesia or analog-sedation becomes more and more clear to the general anaesthesiological audience and there is an increasing awareness that these qualities can be quantified and accordingly used in the frame of a controlling unit that depicts their prevailing interactions.

The theoretical and technical prerequisites for such an IHADS are all available. Infusion pumps that can be controlled by a central computer and thus would act as “slaves” are on the market. Meanwhile, such pumps automatically recognize the inserted syringes by their type, size and filling volume. It only should be implemented. The infusion pumps not only follow delivery orders from the central processor, but report vice versa their actual activity, plunger pressure, and residual volumes. With this, warnings for obstructed infusion lines as well as pending refill of the syringe can be issued on time. The pharmacokinetic algorithms for most intravenous anaesthetics and analgesics, which are at the core of the IHADS, have been worked out more than a decade ago and are freely available. An already advanced drug level course calculation and display is available in the frame of the software TIVAtainer, which also calculates hypnotic-/analgesic drug interactions and projects the interaction-zone into the course of the main hypnotic agent. With this one already has the above mentioned first half of the requested monitor screen display. A similar display as suggested above for the hypnosis-

analgesia interaction matrix is in principle already implemented in the SmartPilot® View by Draeger, where it stands as an isobologram for propofol activity and a surrogate analgesic drug action calculated in remifentanyl equivalents. However, to be a really holistic system, both the hypnotics as well as the analgesic components of all drugs have to be included into the calculation, and most important, these effects have to be summarized in suitable surrogate for a overall hypnotic activity level as well as a surrogate for the overall analgesic level, e.g. as the total hypnotic activity of propofol that is administered together with a benzodiazepine or an inhaled anaesthetic. Otherwise, drugs that have both properties such as ketamine, must lead to separate braking down of their hypnotic and analgesic activity in order to be calculated separately.

The pharmacokinetic profile of inhaled anesthetics is also well known and has been included in simulation software such as “GasMan” [6], although interactions with other drugs aren’t implemented there. However, to my knowledge appropriate algorithms for all possible interactions with these drugs have not yet been calculated or published. A somewhat limited system that controls up to 2 pumps is available with the “Orchestra” (Fresenius) anesthesia drug delivery system. However, this device is still too much based on independent pumps that are connected to a central controlling system; thus resembling to primitive creatures with a developed peripheral nervous system but an undersized brain. In particular, this system is unable to accept information about a manually given drug doses and cannot process data from other drug delivery systems such as vaporizers or drug level monitors such as gas analyzers. In contrast, the herein proposed IHADS concept is based on a powerful central controlling system with dependent delivery systems arranged around it. The strict centralization of the control unit makes repeated programming of several single delivery units unnecessary. Naturally, all actuators which deliver anaesthetic drugs have to be connected to the central control system by standardized interfaces that enable communication both ways. Only such an overall controlling unit is able to acquire various data from multiple sources and to process all available information to calculate total hypnotic and analgesic drug activities and interactions.

To summarize, this plea contains both, the urgent expression of the need for a comprehensive anaesthesia delivery system that encompasses all available pharmacological knowledge about the actually used anaesthetic drugs to be delivered under a central control and command unit, and my eventually naïve astonishment that such an equipment is not yet available. Maybe it’s inappropriate to expect from this pamphlet to move the industry somewhat in the desired direction, but at least it might ignite a discussion among the anaesthesiological professionals about the necessity and potential of such a device.

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discussions with representatives of such companies to gauge their ability and interest in developing an IHADS thus not yet leading to substantial results.

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**Legends for the Figures**

Fig. 1: Graphic representation of an independent holistic anaesthesia delivery system. The central processor controls peripheral actuators (solid arrows) and receives feedback from them for their status (dotted arrows). Even manual drug delivery can be recorded by using the keyboard of the inbuilt computer.

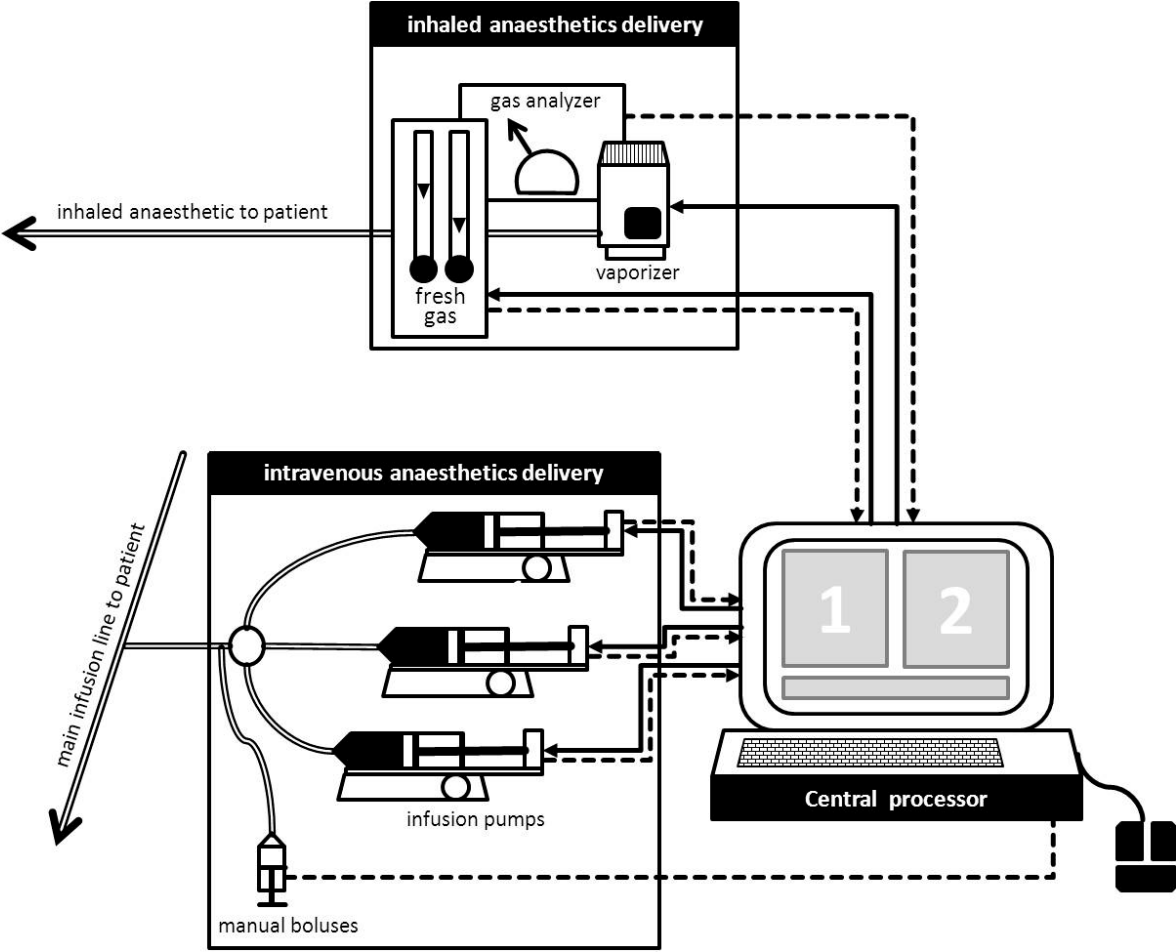


Fig. 2: Structure of the monitor screen composed by 3 windows that display the actual state of anesthetic drug delivery and action. The drug level courses are displayed on the left, the “hypnosis-analgesia interaction matrix” on the right side with the flashing point with its historical trace indicates the orientation of the actual anaesthesia as concerned the overall hypnotic/analgesic activity (image modified from SmartPilot View). The third window at the bottom may contain necessary digital data.

