New Horizons in Drug Delivery

Richard G. Buckles, Ph.D.

Clinical research in chemotherapy attempts to achieve the best practical results by testing new drugs, either singly or in combination with other drugs, or by testing multiple drugs in sequence. Administration is by injection, by pill, or by a one-to-two-hour infusion. This review will consider an alternative approach to testing chemotherapeutic agents that should enhance results.

Continuous drug delivery over prolonged periods has been utilized in cancer therapy, but the results have been inconclusive. This is due to the technical complexity of providing such therapy, which precludes large studies and necessitates many therapeutic compromises. Recent insight into pharmacodynamics has made the latter apparent. This paper will present arguments for a reconsideration of the value of continuous, prolonged therapy, based on recent research and the availability of greatly simplified drug administration procedures.

If one takes the position that more effective therapy may derive from this mode of delivery, two questions must be addressed: (1) What is the evidence in favor of the proposition? (2) Why have oncologists generally neglected continuous infusion?

Evidence of the Value of Continuous Infusion

At least four types of evidence lead to the conclusion that controlled, continuous drug administration over prolonged periods should produce clinical results superior to those attained with intermittent or pulsed delivery. Before examining this evidence, however, we must define our terms. The term "continuous drug delivery" carries the pharmacokinetic implication that this administration procedure continuously maintains effective blood or tissue levels. Since continuous is not the same as constant, the concept includes deliberate variations in delivery rate that, for example, a circadian rationale might require. The word "prolonged" is meant to indicate that duration of therapy is long compared to a single injection; it might, however, be as short as 24 hours or as long as many months.

Clinical Experience

The clinical literature provides little evidence either for or against the value of controlled, continuous administration in cancer chemotherapy. One set of stud-
ies, however, reported on a protocol for the treatment of acute leukemia that required the entire chemotherapeutic regimen to remain constant except for a single factor: duration of continuous and constant intravenous (I.V.) infusions of cytosine arabinoside (Ara-C). Such infusions were provided for periods of two to 10 days; the incidence of patients achieving complete remission (Fig. 1) provided the measure of comparative efficacy of the regimens. The data showed that increasing the duration of therapy from two to 10 days consistently increased the incidence of complete remission.

Pharmacokinetics
A second argument in favor of controlled, continuous administration derives from pharmacokinetic considerations. Pharmacokinetics conjures up a variety of meanings: in the context of developing improved chemotherapy, it provides a way of modeling drug distribution, metabolism, and excretion that permits data obtained in one environment to be extrapolated to rational use in another environment.

There are several ways in which experimental drug effects need to be compared quantitatively in order to improve cancer chemotherapy. Examples would be extrapolations of:
• Quantitative data on the cytotoxicity of drugs from cell cultures to animal models with the same tumors.
• Data on cell kill in animal models to human tumor therapy.
• Data from a single I.V. injection to some other temporal pattern, such as continuous administration.

Pharmacokinetics deals with developing models that are useful in exactly these kinds of situations. While the extrapolations may all require experimental validation, experience has shown that the models increase efficiency of experimental design.

Fig. 1 Clinical evidence that continuous and constant administration of chemotherapy over prolonged periods leads to enhanced results. Studies with Ara-C in induction therapy for ALL.
The literature lacks clear examples of the extrapolation of data on drug dynamics from animals to man, but it does provide at least one good example of correlating toxicity data for a single drug between two animal species. Fig. 2 presents the estimated blood levels in rats and mice dosed with methotrexate at their respective LD50 values by single injection. The LD50 dose for the rat is only about one-sixth of the LD50 dose for the mouse. On the other hand, the pharmacokinetic model of these animals shows that their blood levels at the LD50 dose are virtually identical. That is to say, what appears to be a variation between species in drug effect (LD50) is, instead, simply a difference in the pharmacokinetics of the drug in the two animals. That is, at the two doses, pharmacokinetic modeling reveals that both animal species are exposed to identical concentration-time exposures, which logically has led to comparable toxicity.

What therefore, does pharmacokinetics suggest about continuous administration? Very simply it says that a drug with a very short half-life in the human requires administration for prolonged periods to maintain the blood level at or above some defined cytotoxic value. Substantial disagreement prevails about what the appropriate plasma concentration is, and whether the therapeutic level is lower than that producing toxicity to the host; nevertheless, pharmacokinetic principles certainly argue that continuous delivery provides the only way to keep a constant blood level.

Table 1 is a summary of pharmacokinetic data on some drugs actively used in cancer chemotherapy. These data provide convincing evidence that many antineoplastic agents exhibit a short half-life compared to their current frequency of administration.

**Cell Kinetics**

The third perspective is gleaned from the study of cell kinetics. The action of drugs used to attack cells in culture is expressed through a concentration effect and, in many cases, a time effect. These may be totally independent, as clearly illustrated in the work of Shimoyama et al (Fig. 3). He examined a variety of drugs in several different cell culture lines, each exposed to varying doses for varying durations (one-half hour to 11 days); the surviving fraction of each culture was measured. The important conclusion was that responses to drugs are of three characteristic types. The traditional response anticipated from first-order kinetics for alkylating agents
| Drug             | Half-Life (minutes) | Dose Range       | Ref |
|------------------|---------------------|------------------|-----|
| ACTINOMYCIN D    | ~20                 | 10-15 µg/kg      | 40  |
| ADRIAMYCIN       | ~120                | (1)              | 2   |
| ARA-C            | 12                  | 100 mg (Injection) | 42  |
|                  | 7                   | 210 mg/24 hr (Infusion) | 42  |
| L-ASPARAGINASE   | 27.5 hr             | 500 IU/kg        | 10  |
|                  | 8-30 hr             | 500-100,000 IU/kg | 18  |
| BCNU             | Mouse: <5           | Animals: 10 mg/kg | 13  |
|                  | Dog: <5             |                 | 27  |
|                  | Monkey: <5          |                 |     |
| BLEOMYCIN        | 16-45               | 0.9 mg/M² (2)    | 39  |
| CCNU             | Mouse: 6            | 0.7-2.4 mg/kg p.o. (2) | 27 |
|                  | Dog: <15            |                 | 38  |
|                  | Monkey: <15         |                 |     |
| CYCLO-C          | 28 hr (measured as Ara-C) | 4.9 mg/kg (2)   | 19  |
| CYCLOPHOSPHAMIDE | 405                 | 2.4-24 mg/kg (2) | 7   |
|                  | 275-370             | 0.02-10 mg/kg in single doses OR 2 mg/kg/day for 22 days | 25  |
|                  | 416                 | 50-100 mg        | 24  |
| DACARBAZINE      | 19                  | 6 mg/kg (2)      | 23  |
| DAUNORUBICIN     | ~18.5 hr            | 4.2-5.0 mg/kg (2) | 20  |

* All data presented are for humans, unless otherwise specified.
(1) Not available from reference.
(2) Dosage converted from units of mg/M² using a factor of 1.7 M²/70 kg man.
| Drug                  | Half-Life (minutes) | Dose Range                     | Ref |
|-----------------------|---------------------|--------------------------------|-----|
| 5-FU                  | 12                  | 15 mg/kg                       | 15  |
|                       | 10                  | 15 mg/kg                       | 8   |
| HEXAMETHYL-MELAMINE   | 13 hr               | (1)                            | 43  |
| ISOPHOSPHAMIDE        | 6.3-8.3 hr          | 39-58 mg/kg/day in a 30 min IV infusion (2) | 26  |
|                       | 15.2 hr             | 92-121 mg/kg/day in a 45 min IV infusion (2) | 9   |
| MECCNU                | Mouse: 5            | 2.91-7 mg/kg p.o.              | 27  |
| MELPHALAN             | 105-120             | (1)                            | 31  |
| MERCAPTOPURINES       | 101                 | 5 mg/kg                        | 22  |
| ARA-MP MPR            | 43                  |                                |     |
| METHOTREXATE          | ~157                | 50-500 mg/kg                   | 30  |
|                       | ~120                | 50-200 mg/kg                   | 39  |
|                       | ~45                 | 0.7 mg/kg (2)                  | 21  |
| CIS-DIAMMINE-DICHLOROPLATINUM | 26-49          | 0.066-3.15 mg/kg               | 11  |
| PREDNISONE            | ~195                | 50 mg/day p.o.                 | 12  |
| VINBLASTINE           | 4.5                 | 0.22 mg/kg                     | 28  |
| VINCristine           | Rat: 15             | Rat: 0.1-1.0 mg/kg             | 5   |
|                       | Dog: 13             | Dog: 0.5 mg/kg                 |     |

*All data presented are for humans, unless otherwise specified. (1) Not available from reference. (2) Dosage converted from units of mg/M² using a factor of 1.7 M²/70 kg man.
Fig. 3 The three types of cytocidal effects of drugs tested on cell cultures.4-5
(shown as Type la behavior) is relatively uninteresting; virtually the only effect of increasing duration of exposure is achieving greater kill at a lower dose.

"experimental and theoretical evidence emerges that many chemotherapeutic agents would be more efficacious if administered by continuous delivery."

Type lb and Type 2 are more interesting. Type lb shows that the effective concentration producing a given level of cytotoxicity during an 11 day exposure is lower than that of a 30 minute exposure by a factor of at least 100, if not 1,000. The implication: to avoid the high concentration that produces a particular kind of toxicity, without loss of efficacy, one can extend exposure. The optimum duration will be a balance between the response of normal and tumor cells and their relative rates of recovery from the drug. Type 2 shows that, with short exposure times, cell kill reaches an absolute plateau, beyond which it can rise only through extension of exposure time.

The number of drugs that exhibit Type lb and Type 2 behavior is interesting (Table II). One would expect to see Ara-C and 5-FU under Type 2; but the vinca alkaloids—drugs seldom administered by continuous administration—exhibit similar behavior. Interesting also is the appearance of bleomycin and Adriamycin as Type lb, suggesting that reduced daily delivery rates might greatly enhance their efficacy.*

Toxicity
The final rationale for continuous administration concerns toxicity. Moving from drug delivery via a single dose to continuous administration can have two toxicologic consequences. One is the use of 5-FU infusions to avoid the bone marrow suppression that results from the oral administration of the drug. Here, changing the temporal pattern of administration eliminates the single type of dose-limiting toxicity. Another possible consequence of continuous delivery is reduction of toxicity. Rodriguez et al.6 recently reported that isophosphamide infusions cause less severe hemorrhagic cystitis than injections of the same drug. These examples illustrate the principle that altering a temporal pattern of administration may permit either a lessening of toxicity or an increase in tolerable dosage.

New Infusion Techniques:
Experimental and Clinical
Thus, from four perspectives, experimental and theoretical evidence emerges that many chemotherapeutic agents would be more efficacious if administered by continuous delivery. That leads to the second question concerning continuous drug administration: Why have oncologists generally neglected continuous infusion?

The answer is obvious to anyone who has attempted the procedure. Continuous infusion is one of the most complex types of therapy imaginable. It is complicated technically, in terms of patient safety, and it confronts the issue of human acceptance of a difficult treatment. Trying to keep a patient in bed for five days every month to give a continuous infusion raises serious problems in compliance. New delivery systems, however, should make continuous infusions simpler at both the experimental and clinical levels.

Several types of new technology for delivering continuous, controlled infusions in a fashion that could provide more valid experimental data from animal studies and more humanly acceptable therapy than traditional apparatus have been developed. Three systems that have emerged from this new technology and are being utilized in cancer research and treatment are:

*The reader should be aware that Shimoyama's studies involved a single administration of drug, so the reported dose is merely calculated. No account is taken of drug degradation.
Implantable Minipump for Animal Research

An implantable minipump has been developed to infuse drugs continuously into small animals over a period of a week, after the user fills it with the drug solution. The device is small enough to be implanted in a mouse; it can hold 170 µl of solution.

The minipump delivers its fluid contents at a steady rate of one µl/hr. Water from the external environment is osmotically imbibed into a space around a flexible casing that contains the drug. As water is imbibed, the drug solution is squeezed out through the filling hole. Thus, the system requires only a constant temperature and water activity to deliver its drug content continuously. Fig. 4 demonstrates its behavior both in vitro and in vivo; further details have been published elsewhere.7

Pinedo et al.8 have used the minipump to deliver methotrexate, at constant rates, to cancerous mice to evaluate the dynamic response of several cell types to a constant blood level of drug. The dual mechanisms of methotrexate activity have been clearly distinguished by this method; results of previous studies using injections were unclear, since cells were exposed to both high and low levels of drug during the period of analysis.

Infusion System for Ambulatory Patient Therapy

A lightweight disposable system has been designed to provide continuous intravascular infusion to patients.9 (Fig. 5). The system consists of a cartridge that holds a one-day supply of drug, mounted in a control unit. The latter controls the flow of drug from cartridge to patient. Delivery rate is adjustable from 0.4 to 2.0 ml./hr.; as the infusor is precalibrated, adjustments are easily made by physician or nurse, using a special key. A pharmacist,
180
160
- Slope = 1 μl/hr
140
120
100
80
60
40
20
0

Fig. 4 Cumulative volume delivered from osmotic minipump in vivo and in vitro, indicating a delivery pattern in rats and mice that is similar to the pattern achieved in saline at 37°C.15 (Reproduced with permission of Elsevier Scientific Publishing Co.)

nurse, or doctor uses a syringe to fill the cartridge, which the patient can easily change. The filled infusor weighs only 100 gm., mounts conveniently upon the patient’s arm near the site of cannulation, and uses no electricity.

The cartridge consists of a novel elastometric balloon that exerts constant pressure on the drug solution that it contains. This pressure greatly exceeds venous pressure. Thus, constant drug delivery rates are achievable by use of a stable valve positioned in the control unit between the balloon and the patient.

The low flow rate permits the use of small bore needles or catheters. These provide safe vascular access in ambulatory patients, without influencing the drug delivery rate. A comparison of the in vitro and in vivo flow in 65 patients indicated that ambulation, environmental temperature, or diurnal activity patterns do not influence delivery rate. The in vivo flow rates never exceeded the in vitro calibration rates by more than 20 percent (Fig. 6).

The infusion system contains safety features unattainable in conventional apparatus: (1) a 0.2 μ filter, housed in the control unit; (2) failsafe construction, to prevent massive infusion of drug in the event of system failure; and (3) closure-resistant tubing, to assure continuous drug delivery.

Transdermal Delivery System For Antiemetic Therapy

The transdermal delivery system works on quite a different principle. Drug is delivered, from a patch placed on the skin, by diffusion into the subcutaneous tissue,
Fig. 5 The infusor for continuously administering parenteral drugs to ambulatory patients.°

where it is absorbed and distributed into the systemic circulation. One such system delivers the antiemetic scopolamine and is mounted on the post-auricular skin of a patient a few hours before exposure to stimuli producing nausea or vomiting in susceptible subjects. Trials have been conducted in environments conducive to motion sickness and more recently among cancer patients receiving chemotherapy. Continuous antiemetic protection has been demonstrated over the period of use of the device[10-11](about three days) without most of the usual side effects of scopolamine.

Figure 7 provides a comparison of the urinary excretion rates achieved with therapeutically effective levels of scopolamine, given either by the traditional process of repeat intramuscular injections or by continuous administration transdermally. The size of the system provides a means of varying the plasma levels achieved.

This is an example of a therapeutic system with a fixed pattern of drug delivery. Such systems can be developed only when one can demonstrate the therapeutic advantage relative to a particular pattern. It is the thesis of this presentation that such patterns can be identified for the antineoplastic drugs through research utilizing new, continuous-infusion apparatus of the types described. Only then may we proceed to develop therapeutic systems for cancer therapy.
Fig. 6 The in vivo delivery rate achieved with the infusor during 5-day therapy with Ara-C in ambulatory patients in remission from acute leukemia.

Note: The Valve Indicator Setting is adjustable in increments of 0.2 ml/hr

Fig. 7 The transdermal delivery system achieves constant excretion rates of scopolamine, which are related to the blood levels of the drug. Repeat injections are seen to result in widely varying excretion rates.
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THE LANGUAGE OF MEDICINE

The profession of medicine did not in ancient times concern itself with anything remotely resembling surgery; hence the passage in the Oath of Hippocrates, "I will not perform lithotomy, but will not interfere with those who do." The lancing of boils, the suturing of wounds and the extraction of calculi and foreign bodies, as well as operative dentistry, were the province of the so-called barber-surgeons. Unlettered and often itinerant, these practitioners probably did more good in their way than the erudite and cultivated but woefully ineffectual physicians, who chattered learnedly about peccant humors and restorative purges but often declined even to touch their patients.

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