Chapter 1

NeuroPharmacology: As Applied to Designing New Chemotherapeutic Agents

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Additional information is available at the end of the chapter

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Abstract

Neurooncology anticancer drugs are no exception—their distribution and tissue interactions follow the general rules of classical pharmacology. In an attempt to assist with the new therapeutic approaches to manage cancers involving the central nervous system, classical chemobiodynamic compartment and pharmacokinetic models are discussed and illustrated. In addition, strategies and approaches for penetrating the blood brain barrier (BBB) are reviewed and modeled. Finally, in support of classical pharmacology, a new anticancer agent in clinical trial for brain tumors is reviewed as an example of clinical onco-neuropharmacology.

Keywords: neurooncology, pharmacology, chemotherapeutics in clinical trials

1. Introduction

A basic assumption in cancer management is that all cancer cells must be killed or removed. When surgical and radiotherapies fail to achieve this goal, anticancer agents become the hope for control of the advanced disease.

Classically, when a drug is injected or orally administrated, ideally it is 100% absorbed and enters the systemic circulation and distributed into the various body compartments. The drug then develops equilibrium (distribution) between metabolism, storage, target tumors, nontumor organs, and final elimination [1].

The various body components and physiological barriers, which a cancer chemotherapeutic agent encounters from the time of administration until reaching the target site—the tumor—are depicted in **Figure 1** [2, 3].

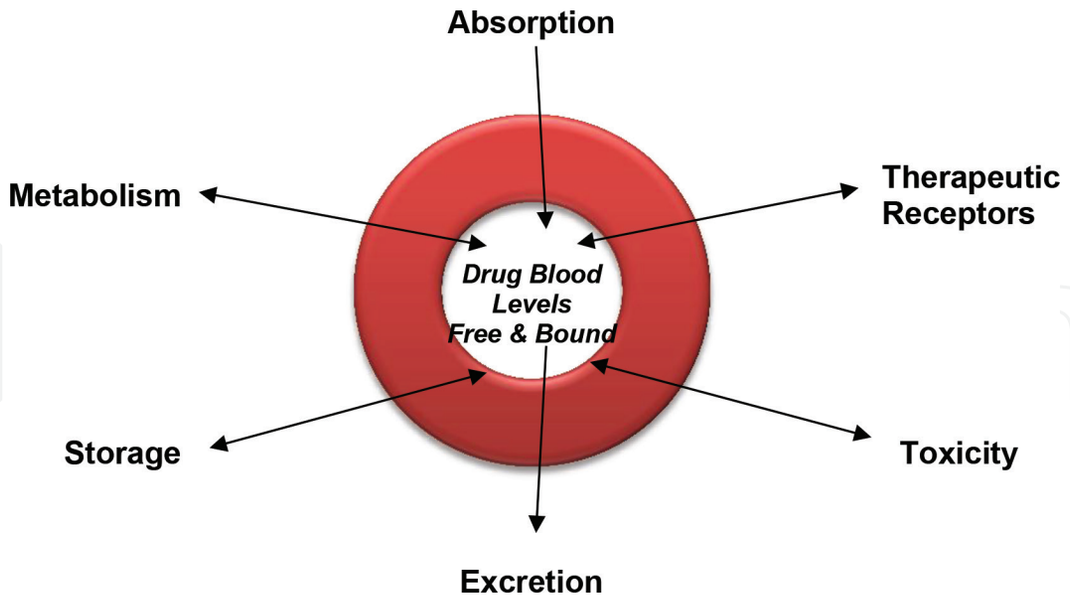

Figure 1. Drug distribution.

The intensity and duration of drug action at any one site depends upon absorption, distribution, affinity, excretion, and metabolism for the drug.

It is anticipated that the drug's tumor selectively will be such that it is absorbed preferentially, with relatively low toxicity to the host organs, such as bone marrow, liver, kidney, gastrointestinal tract, etc. In addition, the accumulation of drug in the tumor will depend upon lipid storage, metabolic activation, and elimination. The liver has a principal role in the metabolism of cancer chemotherapeutic agents, but the other organs such as bone marrow, liver, intestines, kidneys, and even brain also contain low levels of drug-metabolizing enzymes [1, 2].

Table 1 outlines the major types of biotransformation which anticancer drugs can be expected to undergo. These include oxidative, reductive, and conjugation reactions, which usually result in increased product polarity. The resulting product(s) are either activated or detoxified metabolites of the parent drug. The conjugated reactions usually result in water-soluble products, which are excreted *via* the biliary and urinary systems.

Oxidation reactions	Reductive reactions	Conjugation reactions
Aromatic hydroxylation	**1.** Keto reduction	**1.** Glucuronides
1. O^-, N^-, S^-, De-alkylation	**2.** Nitro reduction	**2.** Ethereal sulfates
2. Alkyl chain oxidation	**3.** Azo bond cleavage	**3.** Mercapturic acids
3. S-Oxidation		**4.** Amino acid conjugates
4. Oxidative deamination		**5.** Acetylated aromatic amines

Table 1. Biotransformation of drugs [4].

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2. Cancer Cells Involving CNS

Cancer cells are the target of cancer chemotherapeutic agents, and the rate at which cancer cells interact with these agents is controlled by the hierarchy of molecular organization shown in **Figure 2**.

However, for tumor cells colonized in the brain and associated central nervous system structures, drugs/chemicals have an "additional hurdle," they must penetrate the blood brain barrier (BBB) before classical interactions and pharmacological principles can be applied. Evidence supports anticancer agents exerting their antitumor activities *via* cytotoxic, cytostatic and/or initiating immunotherapeutic mechanisms of action resulting in cancer cell death. All the chemotherapeutics interfere/interact with pathways in the cellular organization (**Figure 2**), thus inhibiting the synthesis of cancer cell DNA, RNA, proteins, and initiating lymphocyte—cancer cell recognition.

Although chemotherapeutics have their initial interactions on the molecular levels, they must first reach their targets. Thus, the abilities of chemotherapeutic agents to reach and interact with their targets are controlled by the hierarchy of distribution (**Figure 1**) and disposition (**Table 1**). These responses or changes are then transmitted to the respective molecular and/or cellular levels of cells (**Figure 2**).

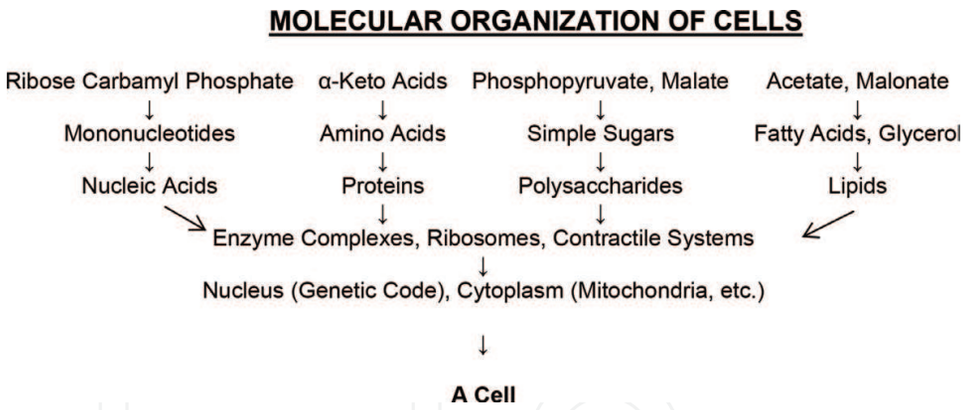

Figure 2. Hierarchy of cellular components. Molecular organization of cells.

3. Clark's correlates

In his classic work on general pharmacology, A.J. Clark divided the possible quantitative drug action(s) into five types [4]:

Relationship between:

(1) Time and the production of some quantitative response.

(2) Time and the incidence of some "all-or-none effect."

(3) Concentration and time of appearance of a selected action.

(4) Concentration and amount of quantitative response.

(5) Concentration and incidence of all-or-none effects.

The first three classes of Clark's correlates are expressions of kinetics and are the rate(s) of actions for drugs, while the last two classes summarize equilibrium conditions between drugs and their target sites. The reactivity of an agent with a molecular target in a biological system, is dependent upon the concentration of the "active therapeutic available" and often more important, is the rate at which the active form of the drug finds its way to the therapeutic sites/targets.

The selection of an optimal drug source requires consideration of:

(1) The qualitative and quantitative nature of the drug's known toxicity.

(2) The influence of drug concentration with time on tumor cell kill.

(3) The drug's pharmacology.

Consideration is also required for recovery time for the target organ, as well as nontarget organs, such as the bone marrow and gastrointestinal tract to recover prior to the administration of additional drugs. This depends on the pharmacologic disposition of the drug, since absorption, distribution, elimination, and metabolism affect the toxicity and efficacy, which can be achieved in the treatment of cancer.

4. Pharmacokinetics

Since most aspects of pharmacology involve dynamic processes, it is necessary to consider the rates or time courses for this process [5]. Pharmacokinetics is the quantitative measurement of concentration *vs*. time for drug and metabolite(s) in respective biological fluids, tissues, and for excretion. Pharmacokinetics is not the measurement of a solution to a problem; it is merely the scientific analysis of a drug's chemobiodynamics— the distribution of a drug in an organism [6].

Common questions in which applications of pharmacokinetics have proven to be useful include:

(1) How a drug is eliminated and how fast?

(2) What factors affect the rate of elimination?

(3) What is the optimal drug regimen for a drug?

(4) How can drugs and radiotherapy be combined?

(5) Is the pharmacological response due to the parent drug or a metabolite?

(6) Does drug distribution change with multiple dosing?

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(7) How do the pharmacokinetics of chemically related drugs compare?

(8) How are the pharmacokinetics of a drug altered by the simultaneous administration of a second drug or radiation?

The initial step in a pharmacokinetic study is to determine if a drug is distributed by first or second-order reactions. The second step is to develop models for documentation.

4.1. First Order Kinetic Reactions

First-order reactions usually produce parallel curves for different doses of a drug with proportional shifts in the ordinate. If not, one must determine, which saturation processes or enzymatic reactions or zero order reactions are present.

Once the reaction kinetics is found to be first order, a model must be formulated. Models are based on the concepts of compartments. The simplest first order pharmacokinetics normally fits a one compartment model; for example, a drug is administered by intravenous injection and eliminated only in the urine or some other single route.

The rate of disappearance of the drug from the blood is proportional to the actual concentration of drug (x) in the blood (**Figure 3**).

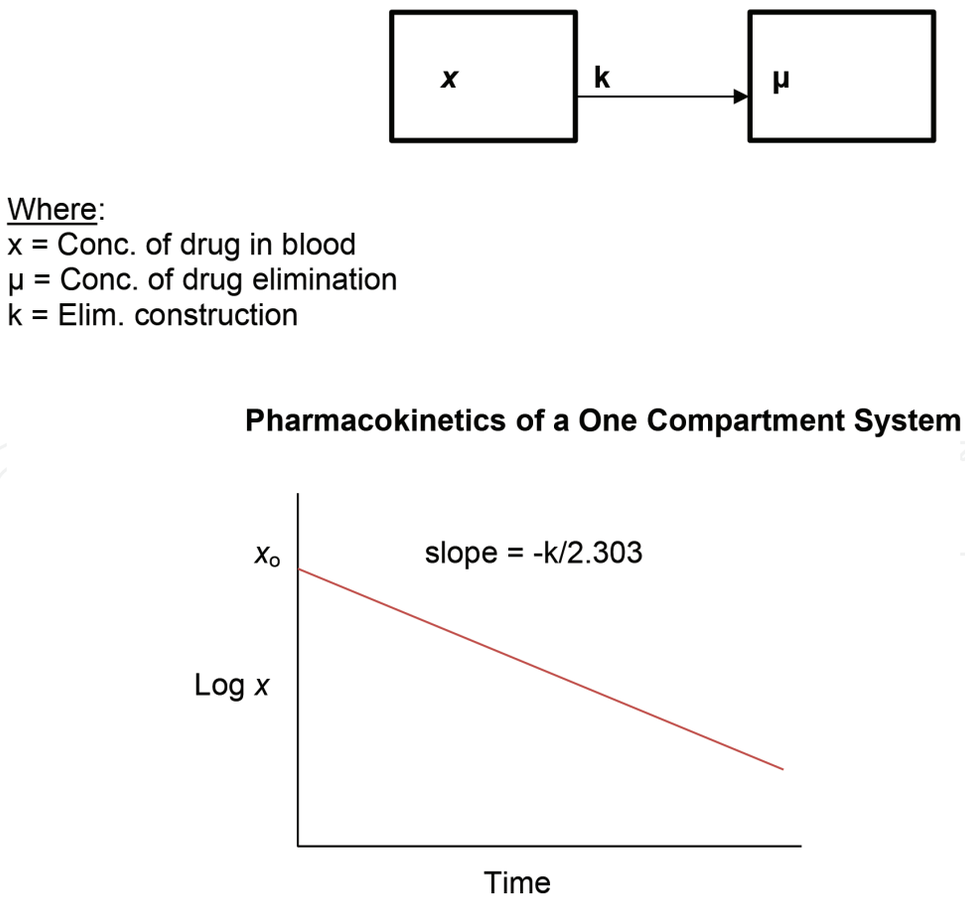

Figure 3. Pharmacokinetics of a one-compartment system.

Plotting the log [x] *vs*. time produces a slope equal to: −k/2.303.

The half-life ($t_{1/2}$) of the drug (x) is the time in which the concentration in the primary compartment decreases by 50%:

$$t_{1/2} = 0.693/\text{k}$$

The half-life is only meaningful as long as there is a one compartment model and the reaction is first-order. The half-life is also related to the clearance (Cl) and distribution (V_d) of the drug:

$$t_{1/2} = 0.693\ V_d/\text{Cl}, \quad \text{where } Cl = k \times V_d$$

and

$V_d = \text{dose}/x_0$; x_0 is obtained by extrapolating the curve to $t = 0$.
Also $-t_{1/2} = 06.93/\text{k} = 0.693\ V_d/Cl$, where: $Cl = k\,V_d$ and $V_d = \text{dose}/x_0$.

Thus, the elimination is calculated as $-dx/dt = -kx$ (with k = elimination constant)

4.2. Second Order Kinetic Reactions

Second-order reactions are best described in models where there are both elimination and distribution to other compartments and the curve would look like **Figure 4**. The upper portion of the curve represents distribution, while the lower flatter portion represents elimination [7].

The slope of the elimination phase or β is calculated by extending or extrapolating the lower portion of the curve to the ordinate (intercept) at B. The slope of the distribution phase or α is calculated by taking the differences between times for actual curve A and extrapolating to (B) back to T_0.

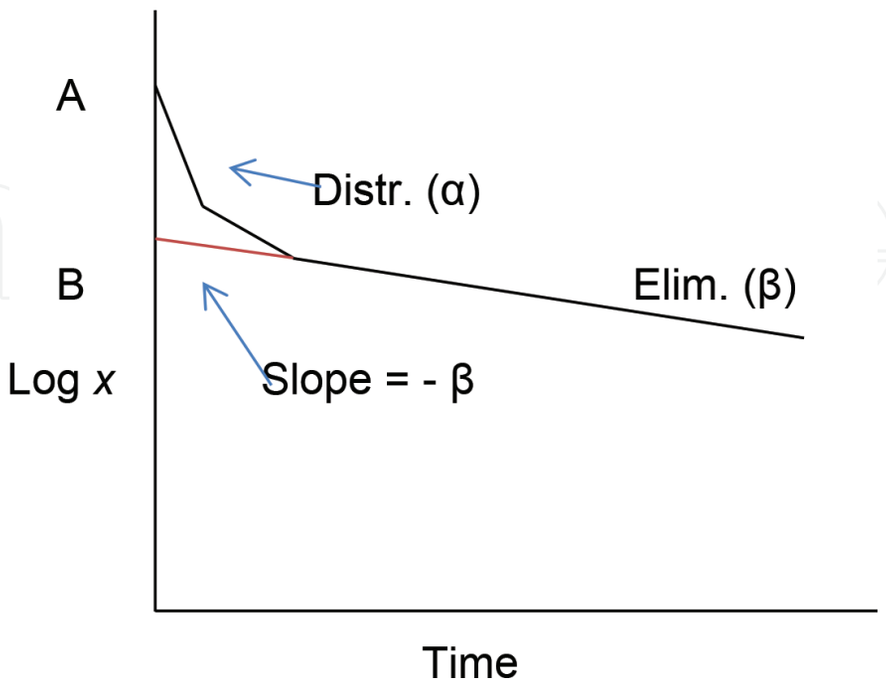

Figure 4. Pharmacokinetics of a two-compartment system [2].

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Here, $t_{1/2}$ (α) = 0.693/α and $t_{1/2}$ (β) = 0.693/β – **Figure 4**.

There are some disadvantages to this type of feathering—data can be biased when converting from linear to log scale and objectivity lost (too much importance placed on the terminal part of the curve where there is often least confidence). Computer models are best employed, if possible.

In this type of example, it is meaningless to speak of $T_{1/2}$, since the whole curve is determined by two $T_{1/2}$ values analogous to K_1 and K_2, and one cannot combine these two values directly. It is no longer true that the $T_{1/2}$ values remain constant for greater than two compartments.

4.3. Drug Distribution

Another reason for the success or failure in drug activity is related to the pharmacologic disposition of drugs in subjects. Even if the tumor is sensitive to a drug, the latter is not useful unless it reaches the tumor site and remains there in cytotoxic (therapeutic) concentrations long enough to kill the tumor cells. In general, the purpose of pharmacology studies is to inform the treating physicians what is an effective concentration (C) of the drug that can be administered by a certain route and be present (available) for a sufficient period of time (T) to bring about the desired effect. This is referred to as the "optimal $C \times T$," and in most diseases, this can be approximated for dosing in humans through preclinical studies in animal models. Generally, 10% of the LD_{10} in mice is the acceptable starting dose [1].

4.4. Correlation of Pharmacokinetic Profile

What makes cancer different from other diseases is the need to relate optimal $C \times T$ to the phases of the cell cycle [1]. First, the optimal $C \times T$ for the tumor must be estimated for the real target—the tumor cells that are susceptible to be killed by the drug. Second, calculations are required to define the optimal $C \times T$ for human safety (e.g., the $C \times T$ that will be tolerated by normal organ tissues (bone marrow or gastrointestinal tract in most cases). Third, the cell population kinetics of both tumor cells and normal cells will be perturbed as a result of the drug's administration; however, the cancer cell growth fraction should be reduced to a greater degree, with sparing of normal tissues. Thus, the potential for drug's usefulness is a balance between anticancer activity and damage to healthy organs/tissues. Understanding the failure of active drugs to cause regression of cancer will depend to a significant extent upon successful delineation of this complex pharmacology.

Thus, the effectiveness of an antitumor agent is directly related to $C \times T$, which is markedly affected by dose, schedule, and its pharmacokinetics discussed above. The sensitivities of the cancer cells, as well as, normal tissue to drugs are the variable factors, which determine the potential usefulness of a drug. Documentation of the optimal $C \times T$ is usually conducted in Phase I studies and will relate clinical responses to acceptable doses and schedules necessary to standardize drug use in humans.

The optimum $C \times T$ should kill the maximum tumor cells with minimum lethality to cells of normal tissue.

The $C \times T$ product is also known as the area under the curve (AUC) and discussed and illustrated latter in this chapter.

5. Blood brain barrier

The chemobiodynamic relationship of a drug with the blood brain barrier (BBB) evaluated using *in vivo, in vitro*, and *in silico* (computational) models in attempt to appreciate the best design for novel anticancer agents to be used in subjects with malignant tumors involving the brain and central nervous system.

The blood brain barrier was discovered over 100 years ago by Paul Ehrlich who found that water soluble dyes stained all organs of animals except for their brains and central nervous system (CNS) [8]. Subsequently, other researchers found that Ehrlich's dye injected into the brain did not enter the blood stream and hence a barrier existed between the two compartments. These compartments could be traversed by more lipophilic substances however [9]. In general, more lipid soluble drugs can traverse the blood brain barrier by passive diffusion, while other molecules can cross the blood brain barrier (BBB) by active transport by proteins such as P-glycoprotein (P-gp) [10].

The BBB differs from normal capillaries in that it has tight junctions in the endothelial cell walls with specialized pores and junctions (formed by terminal surfaces of endothelial cells, neurons, astrocytes, etc.) that allow selective transport through the openings. The BBB is also highly electrically resistant confirming that it is very fatty and free of aqueous electrolytes [5].

To treat cancers involving the CNS, the BBB is the protective "no man's land" must be penetrated by anticancer agents. **Figure 5** depicts two modes of drug transport into the brain and intracerebral cancers. **Figure 5(a)** requires drug to penetrate *via* diffusion or a transfer pathway [12]. **Figure 5(b)** allows drugs to penetrate the CNS *via* the association with RBCs or transport through cancer-associated breaks in the BBB [11].

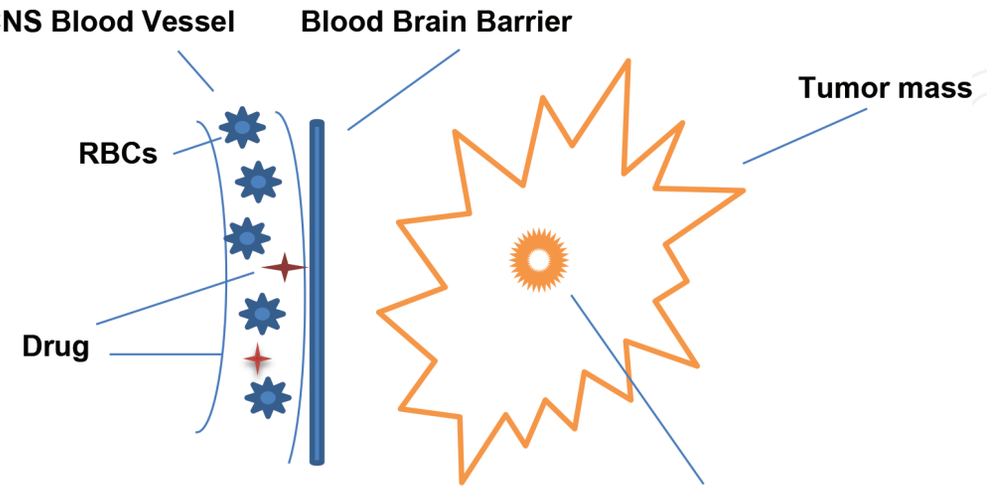

Figure 5a. Primary tumor mass involving the CNS. Drugs (✦) can only penetrate the BBB by passive diffusion or active transport.

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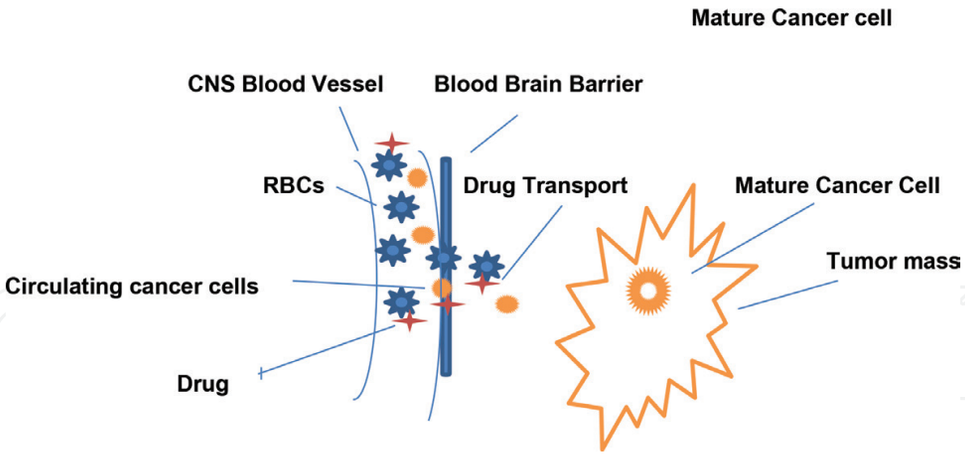


Figure 5b. Breaks (leaks) in the BBB 2° to cancer cell (●) penetration and tumor growth allow RBCs (✹) and associated drugs (✦) easily penetration into tumors growing in the brain.

5.1. Calculation of Log *P*

Measuring or calculating log *P* is the most important molecular attribute to defining lipophilicity and the ability of the drug to diffuse across the lipophilic BBB. This is measured by dissolving the drug in octanol and then shaking with equal volumes of water. The concentration of drug is then measured in both phases and the ratio of octanol-water is calculated according to Eq. (1) [6].

$$\log P_{\text{octanol/water}} = \log\left(\left[\text{solute}\right]_{\text{octanol}} / \left[\text{solute}\right]_{\text{water}}\right) \quad (1)$$

Since, very lipophilic compounds tend to be highly lipoprotein bound and associate/bind to lipid membranes, thus the ideal octanol-water partition coefficient for a neurotargeted drug (at pH 7.4) to diffuse from the serum into BBB into the CSF should be ≤ log *P* 5 [2, 12].

The estimation or determination of BBB permeability as $\log_{BBB}$ (the concentration of drug in the brain is divided by concentration in the blood) is accomplished as follows:

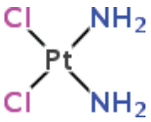
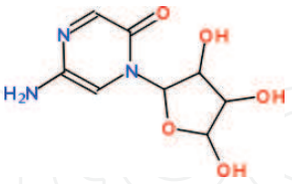
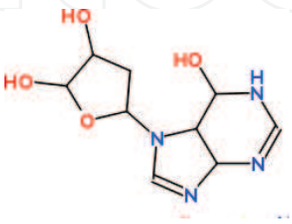
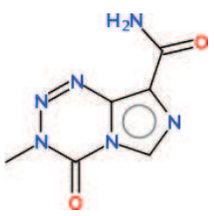
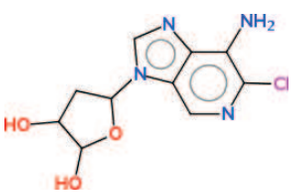
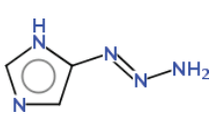
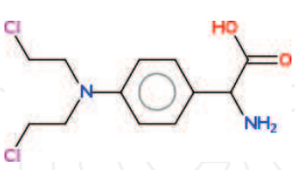
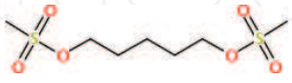
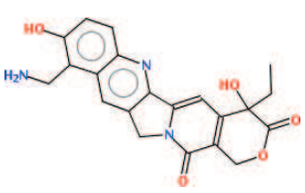
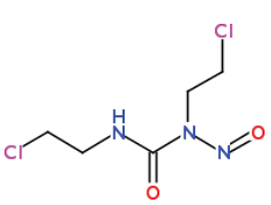
(1) *In vitro* kits to measure $\log_{BBB}$ in monkey or rat brain cells [13].

(2) *In vivo* during a clinical trial (Phase I).

(3) *In silico* computer models that simulate human BBB and are validated by correlating with drugs of known and measured $\log_{BBB}$ values [5]. For example, for DM-CHOC-PEN, temozolomide and others, log P can be calculated from their structure and from Eq. (2) $\log_{BBB}$ calculated [13–15].

$$\log_{\text{BBB}} = \left(\log P - 0/1725\right)/2.808. \quad (2)$$

Table 2 lists compounds with known brain and/or CNS activity and from their structure log *P* is calculated. From this value and Eq. (2) $\log_{BBB}$ is calculated; the latter is compared to literature values in **Table 2**. The calculated and literature values are in good agreement indicating that log *P* is a good predictor of passive diffusion through the BBB. However, one must realize

Compound	Structure	Calculated log *P*	Calculated $\log_{BBB}$	Calculated BBB	Actual BBB [15]
Cis-platinum		−2.83	−1	0.09	0.05–1
Cytarabine		−2.77	−1	0.1	1
Pentostatin		−2.35	−0.9	0.13	0.1-0.13
Temozolamide		−1.9	−0.7	0.18	0.19
Cladribine		−0.38	−0.2	0.64	0.25
Dacarbazine		−0.35	−0.19	0.69	0.14
Melphalan		−0.01	−0.06	0.86	0.01–0.1
Busulfan		0.08	−0.03	0.9	1
Topotecan		1.41	0.44	2.76	0.42
Carmustine		1.67	0.5	3.44	2.3–9

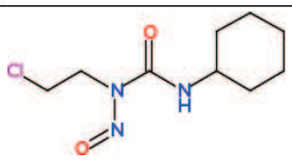
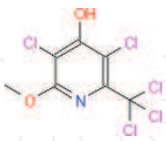
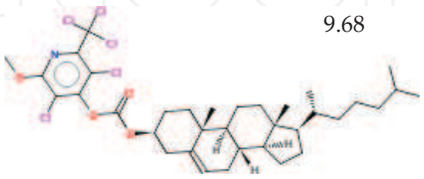
Compound	Structure	Calculated log *P*	Calculated $\log_{BBB}$	Calculated BBB	Actual BBB [15]
Lomustine		2.96	1	10	>0.5
DM-PEN		4.32	1.5	30	TBD
DM-CHOC-PEN		9.68	3.4	2431	TBD

Table 2. Calculated and structure related activities for molecules with known intracerebral activity [15].

that this is just a predictor of drug penetration across the BBB. Some drugs have higher cytotoxicity and selectivity than others and as such are active at lower concentrations than other drugs, e.g., temozolomide. Other caveats include the fact that drugs that penetrate the BBB can be "pumped out" — P-glycoprotein (GgP), thus the log *P* is not predictive that all drugs will be active [10, 15].

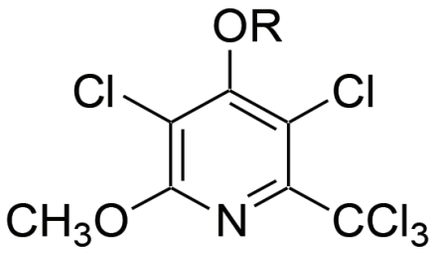
6. Clinical applications

The above introductory information provides the general principles, which must be considered when designing or planning on using a drug to treat cancer involving the brain.

4-Demethyl-4-cholesteryoxycarbonylpenclomedine (DM-CHOC-PEN) [**Figure 6**] is a lipophilic cholesterol carbonate polychlorinated pyridine that is cytotoxic and penetrates the BBB, both because of its $\log_{BBB}$ (**Table 2**), as well as an affinity for red blood cells (RBCs) [16–18].

6.1. DM-CHOC-PEN PK Profile With Cell Cycle

DM-CHOC-PEN's PK profile is best modeled *via* a two compartment model with ~5% being excreted unchanged in the urine [17]. The use of plasma pharmacokinetics is of great importance in considering its use. The drug has produced excellent responses in primary cancers (glioblastomas) as well as metastatic (lung, melanoma, breast) cancers involving the CNS [18]. DM-CHOC-PEN is lipophilic and penetrates the BBB, as well as transported and activated in metastatic cancers involving the CNS through a 4-tier mechanism: (1) transport per RBCs into the brain via breaks in the BBB; (2) entry into cancer cells per the L-glutamine (GLM) transfer system; (3) activation to DM-PEN (active molecule) *in situ* in the acidic microenvironment of cancer cells; and (4) *bis*-alkylation of DNA at N^7-guanine and N^4-cytosine—with cellular death [11].



Where:

DM-CHOC-PEN: R=CO_2-cholesteryl

DM-PEN: R=H

Figure 6. DM-CHOC-PEN and metabolite DMPEN.

It's a large molecule and if there are liver metastases or other hepatic disease involving the liver there can be biliary congestion resulting in reversible jaundice [17].

The pharmacokinetics of DM-CHOC-PEN's disappearance from plasma after a single intravenous dose consist of an initial phase having a $T_{1/2}$ of 5 hours and a final phase $T_{1/2}$ of 245 hours (**Figures 7** and **12**). The slow, final phase of DM-CHOC-PEN elimination is the reason for the single high dose schedules that are currently being employed [18].

6.2. DM-CHOC-PEN Degradation

It has been found that the hydrolysis of DM-CHOC-PEN to DM-PEN (**Figure 7**) is the principle route of degradation and elimination of the drug in animals and humans [16].

Results vary with individual patients but on a mass balance analysis 1–10% of DM-CHOC-PEN are excreted unchanged and the metabolite, DM-PEN is excreted 10–100% in the urine. **Figure 8** shows a pattern seen for 12 subjects treated once with 70–85.8 mg/m^2 plasma and urine drug and metabolite levels [17].

6.3. Area under the curve

Increasing the dose of DM-CHOC-PEN increases the plasma concentration of drug and metabolites. The C_{max} increased with the dose giving rise to an increase in area under the curve (AUC) (**Figure 9**). **Figures 9** and **10** combine and summarize the AUCs for DM-CHOC-PEN *vs*. time [16, 17].

6.4. Distribution and elimination

DM-CHOC-PEN follows a standard two compartment model for elimination [17].

The preclinical and Phase I trial results suggest that the brain and central nervous system is targeted, but that all tissues including cancer tumors will absorb drug [17, 19]. So the second step in decreasing DM-CHOC-PEN blood levels is drug elimination. From bioavailability

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kinetic studies, this has found to be about 4%. The third step of elimination is after the metabolic degradation to a more water soluble and excreted as DM-CHOC-PEN. For DM-CHOC-PEN, the drug is primarily eliminated as DMPEN in the urine, which accounts for 57% of the dose on a mass balance basis. The metabolite on average has maximal plasma concentration 14 hours after drug administration (**Figure 8**) [17, 19].

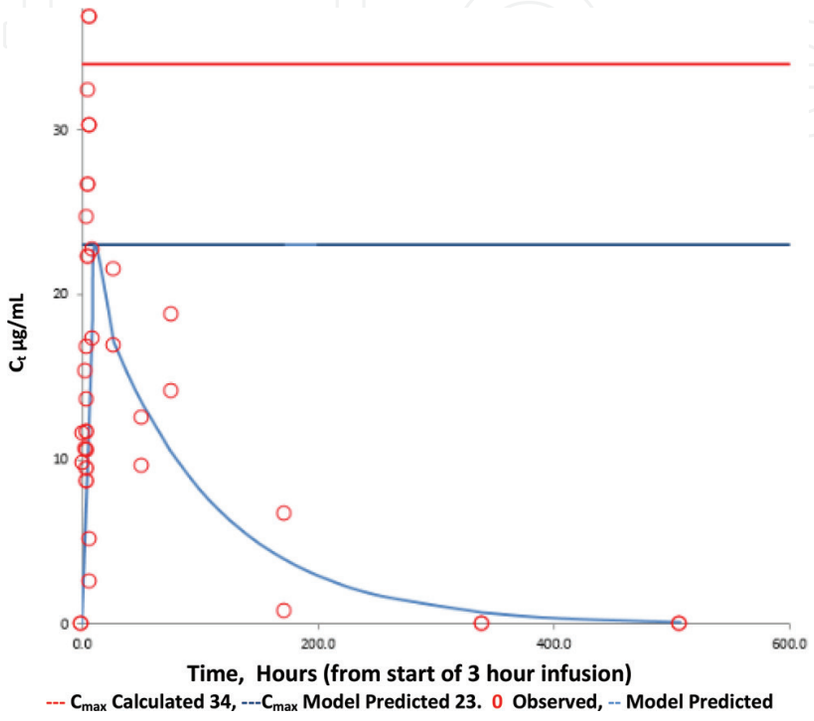

Figure 7. Plasma decay curve for DM-CHOC-PEN: 85.8 mg/m^2 IV once.

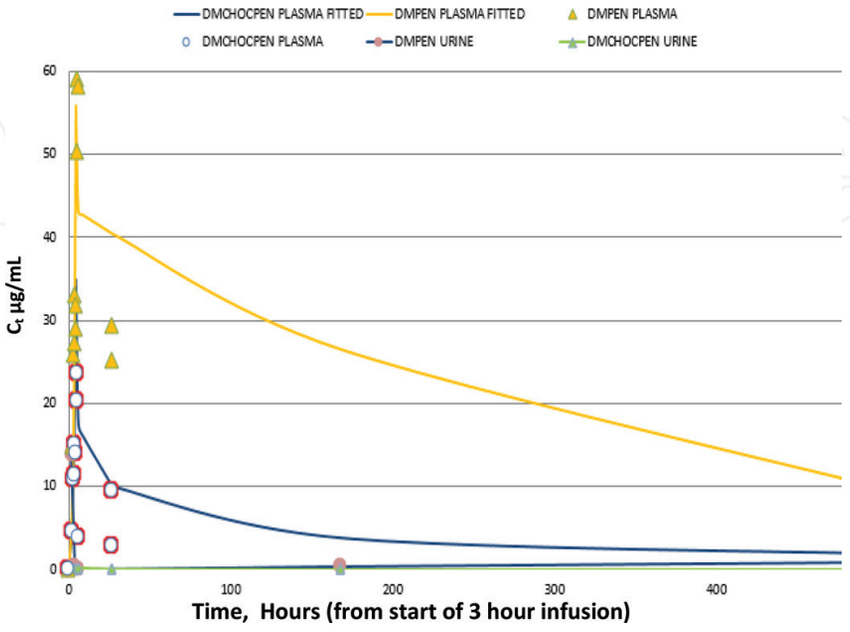

Figure 8. DM-CHOC-PEN + DM-PEN plasma and urine levels.

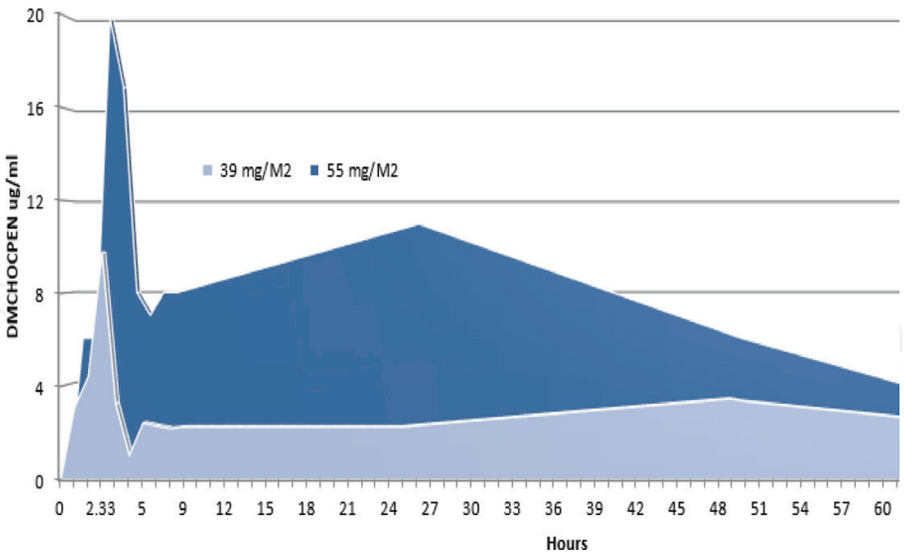

Figure 9. AUC—1 subject–doses of 39 mg/m^2, then 21 days later—55 mg/m^2.

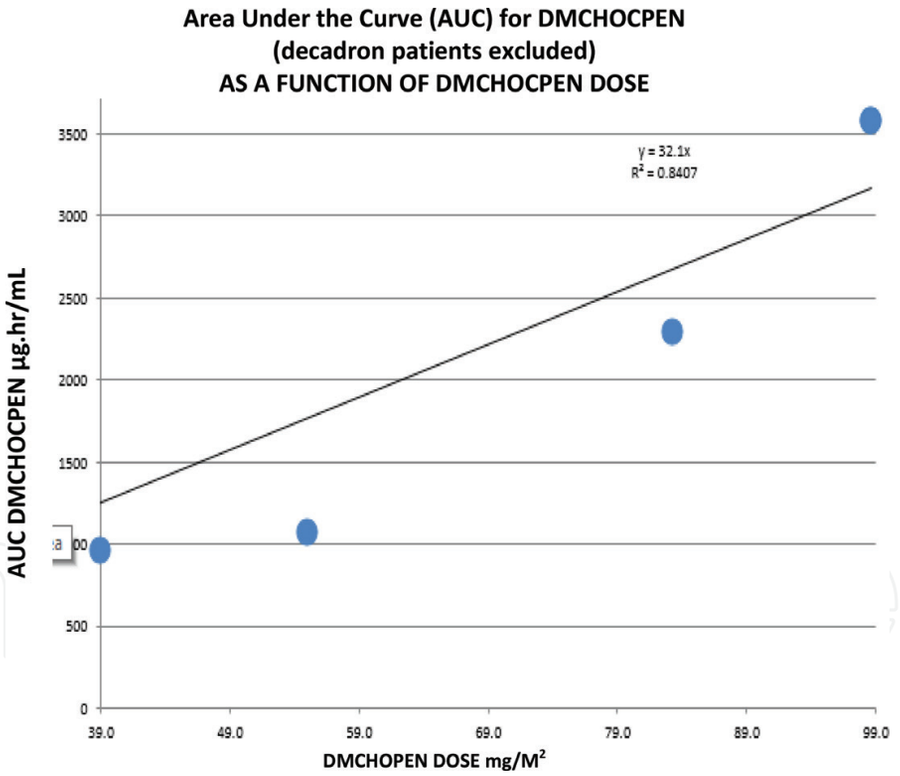

Figure 10. Area under the curve (AUC) for DMCHOCPEN (decadron patients excluded) as a function of DMCHOCPEN dose.

The whole point of the above discussion is to illustrate that there are differing kinetic processes involved in drug elimination such that elimination is not linear with time. In classical pharmacokinetics, this is described as two compartment model and you know you have one when you plot Log Drug Plasma Concentration *vs*. time and you see two slopes (**Figure 12**).

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Thus, from the DM-CHOC-PEN and DM-PEN study, the drug is eliminated in a two compartment model (see **Figures 11** and **12**). In addition, DM-CHOC-PEN has been identified in the CNS and tumors as DNA adducts [17, 19].

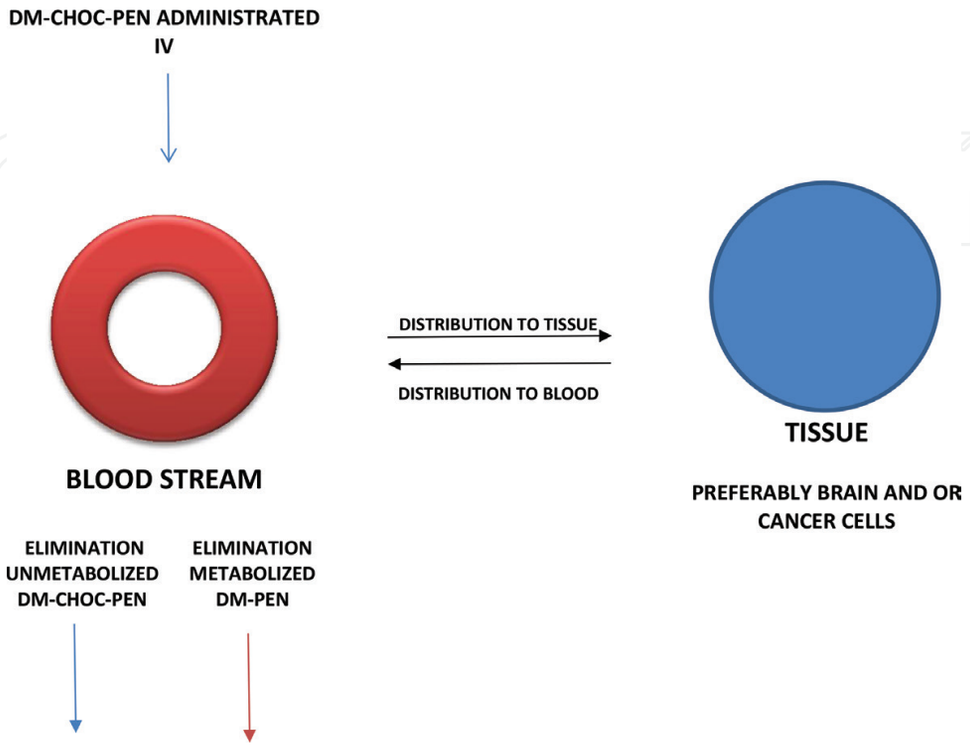

Figure 11. Distribution of DM-CHOC-PEN into the CNS and Cancer Cells.

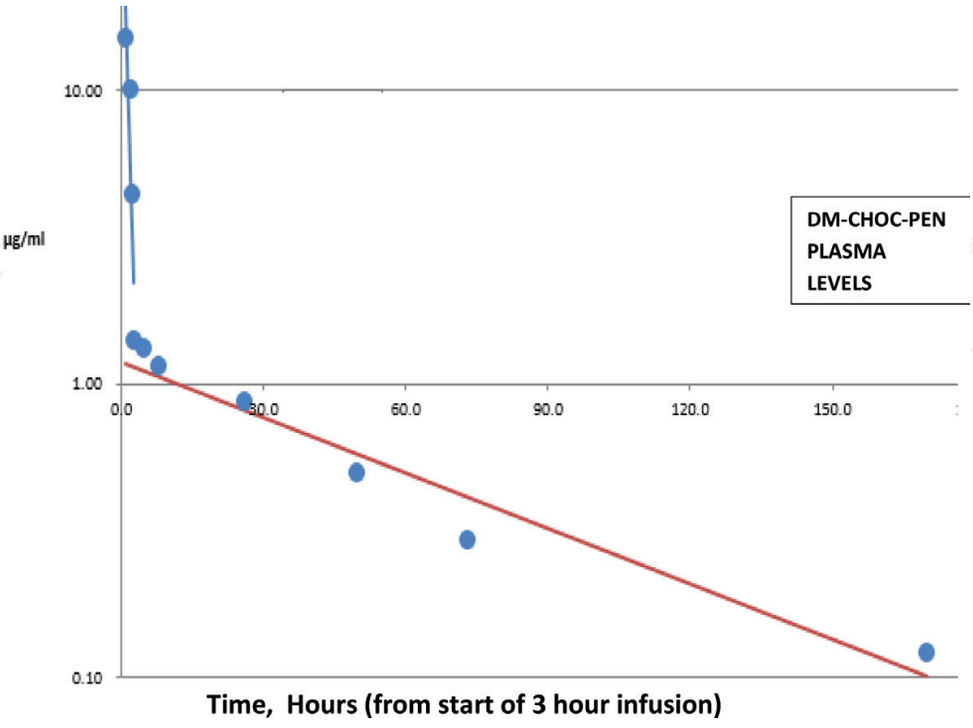

Figure 12. Elimination of DM-CHOC-PEN identified as two-compartment model as log plasma concentration *vs*. time is bi-linear two slopes evident initial α or distribution phase: terminal β or elimination phase.

7. Conclusion

An attempt to review neuropharmacology and distribution of anticancer agents in the central nervous system has been made. However, actually little is known about the interactions of drugs with the various levels of the CNS. We combined drugs in neurooncology but actually know little about the neuropharmacology of any single agent. In fact, Clark's basic pharmacological questions that should have been answered for all the agents we use but have been answered in only a few cases. With the current interests in neurooncology, we may finally make some progress in the specialty—but let's do it correctly.

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