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REVISIONES

Applying *dose banding* to the production of antineoplastic drugs: a narrative review of the literature

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Abstract
The dosage of antineoplastic drugs has historically been based on individualized prescription and preparation according to body surface area or patient´s weight. Lack of resources and increased assistance workload in the areas where chemotherapy is made, are leading to the development of new systems to optimize the processing without reducing safety. One of the strategies that has been proposed is the elaboration by *dose banding*. This new approach standardizes the antineoplastic agents doses by making ranges or bands accepting a percentage of maximum variation. It aims to reduce processing time with the consequent reduction in waiting time for patients; to reduce errors in the manufacturing process and to promote the rational drug use. In conclusion, *dose banding* is a suitable method for optimizing the development of anticancer drugs, obtaining reductions in oncologic patients waiting time but without actually causing a favorable impact on direct or indirect costs.

KEYWORDS
Antineoplastic agents; Administration and dosage; Neoplasms; Quality control

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***Dose banding* aplicado a la elaboración de antineoplásicos: una revisión narrativa de la literatura**

Resumen
La dosificación de los fármacos antineoplásicos se ha basado históricamente en la prescripción y elaboración individualizada según la superficie corporal o peso del paciente. La falta de recursos y el aumento de la carga asistencial en las áreas de elaboración de quimioterapia están propiciando que se desarrollen nuevos sistemas que optimicen la elaboración sin reducir la seguridad. Una de las estrategias que se ha propuesto es la elaboración mediante *dose banding.* Este nuevo enfoque estandariza las dosis de antineoplásicos en rangos o bandas aceptando un porcentaje de variación máxima. Pretende reducir los tiempos de elaboración con la consiguiente reducción de los tiempos de espera de los pacientes, disminuir los errores en la elaboración y fomentar el uso racional de los fármacos. En definitiva, el *dose banding* es un método adecuado para la optimización de la elaboración de antineoplásicos, obteniendo reducciones del tiempo de espera de los pacientes oncológicos, aunque sin llegar a causar un impacto favorable sobre los costes directos o indirectos.

PALABRAS CLAVE
Antineoplásicos; Administración y dosificación; Neoplasias; Control de calidad

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Introduction

The dosing for antineoplastic drugs used for treatment of oncological conditions is typically calculated by using two anthropometric parameters[1]: body surface or weight kilos, except for some specific cases such as carboplatin dosing, which is estimated according to patients' renal function and the target Area Under the Curve (AUC) value, or those antineoplastic agents with fixed dose, such as some tyrosine kinase inhibitors. This historical approach

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requires each antineoplastic intravenous mixture to be prepared in an individualized manner for each patient.

In most cases, chemotherapy cycles are administered out of hospital, and require previous assessment of blood test and renal and liver function, together with other indicators of the clinical situation of the patient, by the Oncologist. This premise is opposed to preparing the mixture before patients attend hospital; that is to say, in a scheduled way. Therefore, the preparation and dispensing of the antineoplastic mixture to Day Hospitals has become a constant challenge for the units in charge of Intravenous Mixture in Hospital Pharmacies.

This situation creates two negative consequences: longer waiting time for patients at Day Hospital, and a higher level of demand for the Pharmacy staff members, who must validate, prepare and dispense drugs with such complex and dangerous management as antineoplastic agents, in the briefest time possible[2].

In recent years, there has been some questioning about the scientific validity of traditional algorithms for individualized dosing, based on body weight and surface[1,3,4]. This fact, together with the acceptance by all professionals involved that a certain flexibility is possible in cytostatic dosing without a significant impact on health outcomes, has been combined with the advantages of preparation by lots in a new approach called *dose banding*.

Concept of *dose banding*

According to the definition by the NECN[5] (*North of England Cancer Network*), *dose banding* is a system whereby, through agreement between all professionals involved in the oncological pharmacotherapeutical process, the intravenous cytostatic drug doses are rounded up or down with the aim to standardize the preparation of antineoplastic drug mixtures, and conduct it under protocol to the highest extent possible[5].

It is recommended that the maximum variation between the exact dose prescribed and the adjusted dose will not be more than 5-10%, either above or below, within some margins which must be previously defined and agreed upon by consensus. The use of *dose banding* to standardize doses within this variation limit is now considered an acceptable practice, with pharmacokinetic studies supporting its similarity[5,6].

The concept of *dose banding* started in the United Kingdom, where it is widely used in order to supply antineoplastic mixtures to oncohematology outpatients. The first experience was conducted by Baker and Jones[7] in 1998, applying this concept to the preparation of methotrexate and 5-fluorouracil. They introduced this system in their hospital as a measure to reduce the long waiting times for Day Hospital patients. As the dose for these two drugs is calculated by body surface, they decided to create 0.05 m^2 intervals; thus, all patients with a body surface between 1.80 and 1.85 m^2 would receive the same standard dose of 1125 mg. Therefore, the maximum variation between the prescribed dose and the prepared dose would never be more than 5%. Baker and Jones[7] reached the conclusion that they could use this system in order to prepare 95% of mixtures of these two cytostatic agents. They pointed out that, with *dose banding*, they reduced waiting times and the volume of waste materials generated during preparation, and they optimized resources in the Chemotherapy Unit.

Models

Since the first experience by Baker and Jones[7], preparation through *dose banding* has been gradually developed and implemented. Currently there are two well differentiated models of implementation in an Antineoplastic Preparation Unit.

British Model

This model was the first to be developed and used in healthcare practice. It is widely followed in the United Kingdom, where it is the cytostatic dosing system used in over 50 hospitals[2].

This model is based in the preparation of low and fixed dose bags or syringes. Following this model, after the prescription of an antineoplastic drug, the adequate number of bags or syringes would be dispensed until the target dose was completed. The maximum number of bags or syringes cannot be more than three per dispensing. The maximum recommended dose variation between prescribed dose and dispensed dose is 5%; though it is accepted that in some specific cases, such as cytostatic monoclonal antibodies, it can reach 10%.

French Model

As a result of the British experience, a French group started to study and implement *dose banding* in French hospitals with good results. The difference with the British model is that no low and fixed dose bags and syringes are prepared; instead, total standard doses are prepared. Thus, only one syringe or bag is dispensed for each medical prescription. The authors claim that with this model there is a reduction in the nursing staff workload at Day Hospital, and any potential mistakes in administration are avoided[8].

This French Model is supported by various pharmacokinetic studies[9] to accept 10% validations between the prescribed and the dispensed dose; some of them will even accept a maximum 20%[10]. In these studies, no significant variations have been confirmed between body surface calculation and *dose banding* for a maximum 10% variation.

The British *dose banding* model is present in a higher number of hospitals, and there are more articles and

Table 1. Dose banding *regimen for 5-fluorouracil by Baker and Jones*[7]

5-Fluorouracil 600 mg/m²			
Body surface (m²)	Calculated dose (mg)	Final dose with *dose banding* (mg)	Variation (%)
1.4	840	875	4
1.45	870	875	1
1.5	900	900	0
1.55	930	900	3
1.6	960	1000	4
1.65	990	1000	1
1.7	1020	1025	0
1.75	1050	1025	2
1.8	1080	1125	4
1.85	1110	1125	1
1.9	1140	1125	1
1.95	1170	1125	4
2	1200	1250	4

guidelines published about it. However, its complex dispensing and a higher likelihood of administration errors at Day Hospital make it inadvisable. The French model reduces dispensing complexity and mistakes associated with administration; therefore, currently it represents the first option in order to develop a *dose banding* model.

Advantages and drawbacks

In order to understand the advantages and drawbacks presented by this new system of drug preparation, surveys have been conducted where healthcare professionals were asked about their opinion. Two publications stand out: the one by Plumridge[2] in 2001, who asked Hospital Pharmacists, and the one by Kaestner[11] in 2009, who asked prescribers.

In the survey by Plumridge[2], conducted in the United Kingdom, questionnaires were applied to Oncology Pharmacists in 13 hospitals where the dose banding system had been implemented for cytostatic preparation. Those pharmacists interviewed supported unanimously the preparation with this system, pointing out that it reduced the pressing speed with which Pharmacy staff must prepare individualized antineoplastic doses. The authors support that an increase in workload within an aseptic environment was creating significant stress in the staff involved in preparation in many hospitals. The respondents perceived that *dose banding* reduced complaints by Hospital Day nurses, by prescribers, and by patients regarding long waiting times. The support by Oncologists to this system was classified as High by approximately 70% of Pharmacists included in the survey. Besides, the respondents identified the following key supporting factors for *dose banding*:

- Reduction in complaints by nurses and Oncologists regarding the extent of time from receiving a prescription in the Hospital Pharmacy and the availability of the cytotoxic drug.
- Reduction in pressure on the Pharmacy staff.

Reduction in complaints by patients due to waiting times at Day Hospital.

- Reduction in medicine waste by incomplete usage of vials when preparing individual doses.
- Higher likelihood of re-using the mixture prepared if its administration is cancelled.

Table 2. Dose banding *regimen following the English Model*[2]

Antineoplastic drug and band range (mg)	Band range (mg)	Standard syringes or bags (mg)	Number of syringes or bags to be dispensed
Fluorouracil 500-1000 1100-1500	 50 100	250, 300, 400, 500, 600, 1000	1-3
Cyclophosphamide 500-1000 1100-1800	 50 100	250, 300, 400, 500, 600, 1000	1-3
Methotrexate 50-100	 5	15, 50, 55, 60, 80	1-2
Doxorubicin 50-120	 5	10, 15, 20, 40, 50	1-3
Epirubicin 50-200	 5	10, 15, 20, 40, 50, 100	1-4
Leucovorin 25-50	 5	5, 10, 25, 40	1-2

Lower cost through preparation by lots and reduction in time of preparation.

– Preparation by lots facilitates the incorporation and standardization of quality controls in the finished product.
– *Dose banding* implementation requires its acceptance by all professionals involved in the pharmacotherapeutical process, including prescribers. There was a published study about the survey on *dose banding* conducted among chemotherapy prescribers, including clinical oncologists and haematologists from the United Kingdom[11] (Table 3). Questionnaires were validated with quantitative and qualitative elements, and mailed to 1,104 prescribers throughout the United Kingdom; 387 responses were received (35%). Many of the participants were concerned about delays in outpatient chemotherapy associated with the individualized preparation of antineoplastic drugs; 81% were aware of the *dose banding* system, and 63% reported that it was implemented in their hospital, to a higher or lower extent.

There were some differences in opinion regarding the maximum dose variation allowed in *dose banding* regimens. Maximum deviations of <5% and <10% were supported by 52% and 40% of respondents, respectively. There was also support for the use of dose banding with monoclonal antibodies used in Oncology, such as trastuzumab.

On the other hand, there are certain disadvantages associated with the use of this system. The first reason mentioned by those opposing this system refers to an increase in variability. When prescribing a cytostatic dose, it is assumed that there will be a random variability in measuring the patients' weight and height, the use of a limited number of decimals in prescription, the volume of cytostatic within the vial, the volume of the dilution bag, and the skill of the person responsible for preparation in terms of transferring the liquid from one container to another. Dose banding adds on one more rate of variability to the dose which will ultimately be administered to the patient.

In the surveys by Plumridge[2] and Kaestner[11], the majority of opposing opinions refer mainly to the increase in total variability for the dose prescribed, and the lack of clinical freedom at the time of deciding the dose administered to the patient. Prescribers highlighted the need for further clinical evidence in order to confirm that there are no differences in therapeutic outcomes between individual dosing and standardized doses.

Finally, there is a drawback which would limit the implementation of this system in the majority of hospitals in our setting. A large part of the electronic programs for cytostatic prescription have no specific function to round up body surface or final dose. Therefore, if this was implemented, it should be done manually by the prescribers or oncology pharmacists, with the significant increase in workload and risk of mistakes entailed.

Types of *dose banding*

There are two main types of *dose banding* that can be used:

Adjusted by body surface

The patient's body surface area is rounded to the first decimal place. For example, for a 600mg/m² dose of 5-fluorouacil in a patient of 1.61 m², the body surface would be adjusted to 1.60 m², and the final dose to be prepared would be 950 mg (Table 4).

Table 3. *Outcomes obtained by Kaestner's Survey among prescribers in the United Kingdom[11]*

Question	Yes	No	Don't know	Not answered
Do you have any concern about waiting time for outpatients?	281 (74%)	93 (25%)	5 (1%)	-
Have you ever heard about *dose banding*?	308 (81%)	71 (19%)	-	-
Does your hospital use *dose banding*?	238 (36%)	83 (22%)	20 (5%)	38 (10%)
Do you think that it is reasonable to use *dose banding?*	308 (81%)	10 (3%)	55 (15%)	6 (2%)
Do you think there are benefits in the use of *dose banding*?	349 (92%)	4 (1%)	7 (2%)	19 (5%)
What do you think would be the maximum deviation allowed from the individualized dose?				
< 5%	197 (52%)			7 (2%)
<10 %	150 (40%)			
<15 %	8 (2%)			
Other	17 (4%)			
Do you find it acceptable to use *dose banding* with antineoplastic drugs not currently using body surface for dosing?				
Carboplatin	203 (54%)	79 (21%)	70 (18%)	27 (7%)
Monoclonal antibodies	232 (61%)	37 (10%)	72 (19%)	38 (10%)

Table 4. Dose banding *regimen for 5-fluorouracil using the English model and based on body surface as recommended by the NECN*[5]

BSA	5-Fluorouracil dosing (mg/m²)					
	300	370	400	425	500	600
1.4	400	500	550	600	700	850
1.5	450	550	600	650	750	900
1.6	500	600	650	700	800	950
1.7	500	650	700	700	850	1000
1.8	550	700	700	750	900	1100
1.9	550	750	750	800	950	1150
2.0	600	750	800	850	1000	1200

Adjusted by final dose

The final dose obtained is rounded up with a pre-defined interval. For example, for a 600mg/m² dose of 5-fluorouacil in a patient of 1.61 m², 966 mg should be administered. As this value falls in the 926 to 975 mg range, the final adjusted dose would be 950 mg (Table 5).

In practical terms there are no significant differences between both methods. Adjustment by body surface is more widely implemented in the British System, because it is perceived as more compatible with daily clinical practice[12].

Antineoplastic agents most suitable for *dose banding*

Not all antineoplastic drugs are suitable for preparation through this system. Three factors can be mentioned as determinant for a cytostatic agent to be adequate for preparation according to *dose banding*[10]:

– Stability of the preparation in dilution
– Frequency of prescription
– Number of bands required

All publications coincide in mentioning as the key determinant the physical, chemical and microbiological stability of the cytostatic in dilution[8]. According to some publications, they should have an expiry of over 30 days[5], although mixtures with an expiry of over 15 days are typically accepted[8].

Besides stability, an essential requirement in order to apply this system for cytostatic preparation is that these should be mixtures typically prescribed. In the article by Pouliquen[10] it is recommended to implement it only in those mixtures with over 250 preparations per year, that is to say, around 5 prescriptions per week.

Dose standardization is very troublesome in those drugs with different strengths. Many bands or standard doses would be required for these drugs, so that their preparation had a good cost-benefit. The least different strengths the cytostatic has, the most beneficial this preparation system will be.

Summing up, dose banding implementation would only be recommended in those cytostatic agents with stability in dilution, a high frequency of prescription, and when five bands or less can cover at least 60% of the prescriptions for said cytostatic agent[8].

The medications that would currently meet these criteria and could be prepared according to the guidelines by the NECN[5] for preparation with this system are:

– 5-Fluorouracil
– Cyclophosphamide
– Doxorubicin

Table 5. Dose banding *regimen for 5-fluorouracil 600 mg/m² based on final dose*[2]

Dose range (mg)	Range (mg)	Standardized dose (mg)	Maximum variation (mg)	Maximum variation (%)
676-725	50	700	25	4
726-775	50	750	25	3
776-825	50	800	25	3
826-875	50	850	25	3
876-925	50	900	25	3
923-975	50	950	25	3
976-1025	50	1000	25	2

– Epirubicin
– Gemcitabine
– Methotrexate
– Carboplatin
– Oxaliplatin

On the other hand, there has been a wide discussion about the application of *dose banding* in monoclonal antibodies used in oncohaematology[11]. It is considered that there are no reasons why this type of drugs would not benefit of dose banding preparation, as long as they meet those requirements previously described for traditional antineoplastic drugs[8].

Application in special populations

There are certain populations in which the *dose banding* system would not be recommended, due to their specific characteristics[5]:

– Paediatric patients. The application of dose banding in paediatric oncohaematology is not prohibited *a priori*. However, some authors[5,6,12] do not recommend it, due to the following reasons:
• More complex dosing. The dose used in treatment regimens may depend on more than one variable (weight and body surface and age).
• High interindividual variability between weight and age.
• Smaller doses would require narrower bands, which would not be effective for preparation by lots.
• Lower population.
– Patients with cachexia or obesity: *Dose banding* would not be recommended for patients with extreme weight (under 45 kilos or over 100 kilos).
– Patients included in clinical trials. Though some clinical trial protocols allow dosing with *dose banding,* this is not allowed in most cases, so it should not be implemented in this population.

Improvements in treatment efficacy

The majority of published studies coincide that using *dose banding* for cytostatic preparation leads to a reduction in patients' waiting time[5-10,13-15] and there is a lower number of mistakes in preparation[13].

However, it is not still completely clear if there is any reduction in direct and indirect costs[16]. According to the British Health Agency, it is estimated that the introduction of *dose banding* would have a minimal impact on the total cost of oncological medicine[5]. However, there could be a reduction in indirect costs for staff and materials. The guidelines by the English NECN[5] recommend an investment in *dose banding* as the first measure to promote savings in Hospital Pharmacies. In a pharmacoeconomic study[16], the cost for each millilitre of antineoplastic drugs purchased was calculated before and after *dose banding* implementation; and this practice reduced the cost for antineoplastic purchase to a significant extent. The authors claim that *dose banding* implementation together with an adequate system of dispensing and traceability could ensure a high percentage of re-use of returned mixtures, with the resulting savings. In any case, the economic impact would depend on the drugs chosen, their frequency of prescription, and the particular characteristics of each hospital. For this reason, the outcomes of published studies cannot be extrapolated to other centres.

It is unquestionable that dose standardization through dose banding would entail major improvements for an Intravenous Mixture Unit:

– Preparation by lots could be conducted. This prospective approach would represent savings in time of preparation, a better utilization of clean rooms in the afternoon shift, and a reduction in preparation mistakes.
– It would also represent a major advance in the training of the unit for preparation for third parties.
– The automation of preparation and the implementation of quality controls would be facilitated in the future.
– It could represent major savings due to a wider recycling of the mixtures returned by hospital wards.

The primary objective of standard preparation by *dose banding* is to reduce waiting times for oncology patients in Day Hospital. However, there are other simpler strategies which should be considered before implementing *dose banding*:

– To conduct medical assessment visits the day before administration of the chemotherapy cycle[17].
– To develop a computer system which prioritizes antineoplastic preparations and is synchronized with the Day Hospital agenda[18].
– To prepare mixtures in a scheduled manner before confirmation by the prescriber, accepting a proportion of losses by cancelation[19].

Conclusions

The implementation of a preparation and dispensing system based on dose banding in a Unit for Antineoplastic Mixture Preparation could be an option to consider in order to reduce waiting times in Day Hospital, as long as other less complex strategies have been previously tried. The following secondary benefits can be expected: a reduction in preparation mistakes, a better re-utilization of returned mixtures, and probably final savings in direct and indirect costs. However, the limitation in the computer system for individualized electronic prescription represents a current barrier for its implementation and development in the majority of centres.

On the other hand, the reduced evidence available and its low quality in terms of outcomes obtained make it necessary to develop more studies in order to confirm the advantages of this preparation system.

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