Clin Pharmacokinet (2016) 55:439–459
DOI 10.1007/s40262-015-0323-x

SYSTEMATIC REVIEW

Therapeutic Concentrations of Metformin: A Systematic Review

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Published online: 2 September 2015

Abstract

Background Metformin has been available since 1957. Over 50 years later, one can legitimately question whether a clear definition of its "therapeutic concentrations" is available.

Objective The objective of this systematic review was to establish whether or not there is a literature consensus on the "therapeutic concentrations" of metformin.

Methods We systematically searched the scientific literature with the keywords "metformin", "therapeutic concentration", "therapeutic level", and "therapeutic range". When the suggested values were defined by citing a literature reference, the types of studies in cited references and the concordance of data between the citations and theirs sources were studied.

Results We identified 120 documents that reported or cited 65 different "therapeutic" plasma metformin concentrations or ranges. The values ranged from 0.129 to 90 mg/L, and the lowest and highest boundaries were 0 and 1800 mg/L. Only four original research studies determined a "therapeutic concentration". Fifty-four publications cited previous studies as defining the therapeutic concentrations, whereas 62 publications mentioned "therapeutic concentrations" but did not even cite a supporting reference. The supporting references were mostly reviews, pharmacokinetic studies and in vitro studies. In the 54 publications that cited references, concordance between the wording of the citation and the true nature of the source data was observed in only 23 cases (42.6 %).

Limitations Given the nature of a systematic literature search, the only possible limitation would be incomplete identification and retrieval of publications on therapeutic concentrations. An extensive study of the literature has, however, been performed by examining nearly 1000 potentially relevant publications.

Guidance for Clinical Practice The only valid way of defining the therapeutic concentration window for metformin would be to relate dose efficacy (in terms of blood glucose control) to the corresponding plasma concentration in long-term treated patients.

Conclusions Although metformin has been available for over 50 years and it is the key medication in first-line treatment of type 2 diabetes mellitus, major methodological and/or conceptual errors have confounded the literature on its therapeutic concentrations.

Key Points

We identified 120 documents that reported or cited 65 different "therapeutic" plasma metformin concentrations or ranges.

Although metformin has been available for over 50 years, major methodological and/or conceptual errors have confounded the literature on its therapeutic concentrations.

A dose-efficacy study with measurement of the corresponding plasma metformin concentrations is therefore needed for defining the therapeutic concentration window for metformin.

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1 Introduction

For any given drug, the physicians should always prescribe the "therapeutic dose"—a dosage corresponding to the "therapeutic range" that provides sufficient efficacy whilst avoiding overdosing. The "therapeutic range" can also be defined as "an approximation of the average plasma drug concentrations that are safe and efficacious in most patients" [1]. However, when studying the dose–response relationship for various dosage regimens, the relationship between blood concentrations and clinical effects may be evaluated in several different ways: (1) in clinical studies from which pharmacological parameters are measured; (2) by deducing the therapeutic range on the basis of pharmacological data; and (3) by combining clinical and pharmacological data on drug efficacy and concentrations. Once a therapeutic range has been defined, one can subsequently define subtherapeutic and supratherapeutic conditions.

Although metformin has been available since 1957 and is recommended as a first-line treatment for type 2 diabetes mellitus [2], this drug provides an excellent example of why therapeutic concentrations must be characterized. On one hand, metformin should be prescribed more widely because of its beneficial, pleiotropic effects. On the other, it should be prescribed less widely because an increasing proportion of diabetic patients have poor renal function—a contraindication to metformin use because of the risk of so-called "metformin-associated lactic acidosis" [3–5].

The first reports on a therapeutic dose and therapeutic concentrations for metformin were published in 1962 [6] and 1972 [7], respectively. Over 50 years later, one can legitimately question whether a clear definition of the therapeutic concentrations of metformin is available. To address this issue, we systematically searched the literature for publications that mention "therapeutic concentrations" of metformin.

2 Research Design and Methods

2.1 Data Sources

We performed a systematic search of the scientific literature recorded in the MEDLINE, Scopus, ScienceDirect, and Wiley-Blackwell electronic databases between January 1957 and November 2014. We also searched the Internet using the Google search engine and performed a manual search in our personal libraries (including documents that are not referenced in the aforementioned electronic databases).

2.2 Data Selection

We used the keywords "metformin", "therapeutic concentration", and "therapeutic range" but also searched for allusions and related wordings such as "therapeutic level", "plasma concentration", and "normal value" with regard to metformin's antidiabetic effects.

2.3 Data Extraction

We extracted values or ranges described as "therapeutic concentrations" from the retrieved documents and their cited references (Fig. 1). When a blood metformin value or range was not defined exactly as a "therapeutic concentration" or "therapeutic range", we cite the original wording of the text. When suggested therapeutic values were defined by citing a literature reference, the types of studies in cited references and the concordance of data between the citations and their sources were studied.

2.4 Data Presentation

All of the collected data are presented in a single table (Table 1), which is rather large but it was impossible to subdivide it into study categories (e.g., in vitro studies, animal studies, clinical studies, etc.). Indeed, this type of categorization might have erroneously suggested that the mentioned "therapeutic concentrations" were deduced from the results of the studies themselves. In fact, most of the "therapeutic concentrations" were suggested by citing other data (either personal data or, more often, a previous publication) and thus were not based on the study's design and results. Furthermore, Fig. 2 serves as a guide to reading Table 1.

In some papers, metformin concentrations were noted in molar or gram units. Here, the concentrations were converted into mg/L if necessary. The exact molecular weight

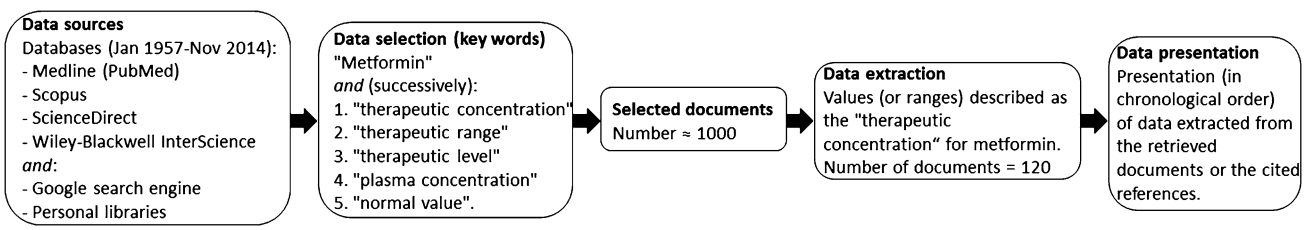

Fig. 1 Flow diagram of data extraction

Table 1 Criteria for therapeutic concentrations of metformin in the literature: values, ranges, wording, and sources

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Frayn and Adnitt [7]	No	Pignard (1962) [9]	10 μg/mL [10]	PKS in DPs	Discordance: the source data were not presented as "therapeutic values" ("plasma ccs were always found <10 mg/L even after an oral dose of 2 g")
Adnitt and Frayn [10]	No	No ref.	10 μg/mL [10]	NA[a]	
Clarke and Ducan [11]	No	Sirtori (1978) [12]	"The plasma concentration following therapeutic dose in man is 300–1000 ng/mL" [0.3–1]	PKS in DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the steady-state plasma ccs range and C_{max})
Isnard et al. [13]	No	Pignard (1962) [7]	<10 mg/L	PKS in DPs	Discordance: cf. Shargel et al. [1]
		Bruneder (1979) [14]	"0.950 mg/L is efficacious blood level for glycemic control"	PKS in DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the fasting plasma metformin ccs)
Mountjoy et al. [15]	No	Clarke (1979) [11]	"The lower and upper therapeutic plasma level observed in man ($1.8–6.1 \times 10^{-6}$ M)" [0.23–0.78]	Review	Discordance (0.3–1 mg/L)
Lambert et al. [16]	No	No ref.	0.225–3.10 μg/L [$0.225–3.1 \times 10^{-3}$]	NA	
Tymms and Leatherdale [17]	No	No ref.	<5.0 μg/mL [<5]	NA	
Wollen and Bailey [18]	No	Beckmann (1971) [19]	For both refs: 5×10^{-5}–10^{-6} mol/L [0.129–6.45]	Review	Discordance: the source data were not presented as "therapeutic values" (citing Inzucchi et al. [2] with different data)
		Noel (1979) [20]		PKS in patients with normal renal function	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters, and incorrect citation of Caporicci et al. [21], itself citing the study of De Lorenzi [22])
Wollen and Bailey [23]	No	No ref.	Up to 5×10^{-5} M [<6.45]	NA	
Bailey and Nattrass [24]	No	Wollen (1988) [11]	10^{-5} mol/L [1.29]	In vitro study (animal)	Discordance (0.129–6.45 mg/L)

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Gregorio et al. [25]	No	Benzi (1986) [26]	"(1.5 μg/mL) i.e. similar to the drug level measured in human plasma after the administration of 850 mg" [1.5]	Measurement of metformin in DPs	Discordance: the source data were not presented as "therapeutic values" ("Metformin concentration 2 h after the last ingestion of 500 mg. Metformin level ranged ~0.05–2.1 mg/L")
Wilcock and Bailey [27]	No	No ref.	10^{-6}–5×10^{-5} mol/L [0.129–6.45]	NA	
Lalau et al. [28]	No	No ref.	<5 mg/L [<5]	NA	
Gregorio et al. [29]	No	No ref.	1.5 μg/mL [1.5]	NA	
		Benzi (1986) [26]	For both refs: "Recent finding have suggested metformin even at ccs ranging from 1.2 to 4.8 μg/mL-which fall within the therapeutic plasma level" [1.5 and 1.2–4.8]	Measurement of metformin in DPs	Discordance: cf. Wollen and Bailey [18]
		Tucker (1981) [30]		PKS in DPs	Discordance: the source data were not presented as "therapeutic values" [they were presented as the PK parameters (C_{max}, etc.)]
Sarabia et al. [31]	No	Pentikainen (1979) [32]	12–100 μM [1.548–12.9]	PKS in non-DPs	Discordance: the source data were not presented as "therapeutic values" [they were presented as the PK parameters (C_{max}, etc.)]
Freisleben et al. [33]	No	Wilcock (1990) [27]	0.5–5 μM [0.0645–0.645]	In vivo and in vitro (in the animal)	Discordance (0.129–6.45)
Bailey et al. [34]	No	No ref.	"ccs (10^{-6}–10^{-2} mol/L) were considered appropriate to investigate therapeutic and supratherapeutic effects" [0.129]	NA	
Bailey [35]	No	No ref.	10^{-5} M [1.29]	NA	
Sum et al. [36]	No	No ref.	Lower therapeutic range (1–2 mg/L)	NA	
Hermann and Melander [37]	No	Marchetti (1987) [38]	For both refs: "1–2 μg/mL (approximately 10 μmol/L) or even lower" [1–2 "~1.29"]	In vivo (in humans)	Discordance: the source data were not presented as "therapeutic values" (they were presented as the plasma ccs)
		Marchetti (1988) [39]		In vivo (in humans)	Discordance: the source data were not presented as "therapeutic values" (they were presented as the fasting plasma ccs)

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Chalmers et al. [40]	No	Bailey (1988) [41]	1–5 μg/mL [1–5]	Review	Discordance: the source data were not presented as "therapeutic values" ("doses of 1500–1700 mg daily, giving plasma metformin levels up to 5 mg/L usually achieve a stable effect in about 1 week")
Galuska et al. [42]	No	Bailey (1992) [35]	0.01 mmol/L [1.29]	Review	Concordance
Denno and Sadler [43]	No	Bailey (1992) [35]	For both refs: "Mouse embryos were exposed to therapeutic ccs (metformin 500–2550 mg per day for 24-48 h. ccs of metformin in culture ranged from 0.15 to 1.8 mg/mL […] blood values have been reported from 2×10^{-3}–1.755 mg/mL" [150–1800]	Review	Discordance [1–2 (∼1.29) mg/L]
		Marchetti (1989) [44]		Review	Discordance: the source data were not presented as "therapeutic values" (they were presented as the plasma ccs after oral administration)
Fischer et al. [45]	No	Hermann (1992) [32]	$\leq 10^{-4}$ M [≤12.9]	Review	No: discordant values [1–2 (∼1.29) mg/L]
		Bailey (1993) [46]		Review	No: source data not presented as "therapeutic values" ("Plasma concentration is maximally 1–2 mg/L (about 10^{-5} M) at 1–2 h after an oral dosage of 500–1000 mg")
Lalau et al. [47]	Measurement of plasma ccs before drug intake in patients undergoing well-tolerated long-term metformin treatment	NA	0.6 ± 0.5 mg/L [0.1–1.1]	NA	
Miao and Smoak [48]	No	No ref.	0–5 μg/mL [0–5]	NA	
Wiernsperger [49]	No	Freisleben (1992) [33]	0.5–5 μM [0.0645–0.645]	Review	Concordance
Stith et al. [50]	No	Wiernsperger (1996) [49]	"Maximal stimulation of insulin action occurred at metformin concentration in the range of 1–10 μg/mL (∼7.7–77 μM) metformin, this concentration is similar to that found to be therapeutic in diabetic human" [1–10]	Review	Discordance (0.0645–0.645 mg/L)

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Sasson et al. [51]	No	Marchetti (1990) [52]	For both refs: ~10 μM [~1.29]	PKS in DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters and fasting plasma ccs)
		Caille (1993) [53]		PKS in non-DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters)
Scheen [54]	No	No ref.	0.5–1.0 mg/L (fasting state) and 1–2 mg/L (after a meal)	NA	
Radziuk et al. [55]	No	No ref.	"Metformin was added at high therapeutic levels (90 μg/mL) to the medium perfusing an isolated rat liver" [90]	NA	
Schulz and Schmoldt [56]	No	No ref.	0.1–1 (0.6–1.3) (μg/mL) [0.1–1 "0.6–1.3"]	NA	
Stith et al. [57]	No	No ref.	~1 μg/mL [~1]	NA	
Lalau et al. [58]	No	Lalau (1995) [47]	0.6 ± 0.5 mg/L [0.1–1.1]	In vivo (in humans)	Concordance
Lalau et al. [59]	No	Lalau (1995) [47]	"Normal overnight value of 0.6 ± 0.5 mg/L (SD) in diabetic subjects chronically taking 850 mg of metformin b.i.d. or t.i.d." [0.1–1.1]	In vivo (in humans)	Concordance
Al-Jebawi et al. [60]	No	No ref.	0.465–2.5 mg/L	NA	
Detaille et al. [61]	No	Wilcock (1994) [62]	20 μmol/L [2.58]	In vivo (in the animal)	Discordance: the source data were not presented as "therapeutic values" (they were presented as the maximum ccs observed after oral administration, from Frayn and Adnitt [7], Gregorio et al. [25], and Wilcock and Bailey [27])
Detaille et al. [63]	No	No ref.	10 μM [1.29]	NA	
Lupi et al. [64]	No	No ref.	2.4 μg/mL [2.4]	NA	
Wiernsperger [65]	No	Freisleben (1992) [33]	0.5–5 μM [0.0645–0.645]	In vitro (in humans)	Concordance
Lalau and Race [66]	No	No ref.	"Plasma metformin concentrations of up to 1 mg/L are classified as normal"	NA	

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Nelson [67]	No	Sambol (1996) [68]	For both refs: 0.5–2.0 μg/mL [0.5–2]	PKS in DPs and non-DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters)
		Scheen (1996) [54]		Review	Concordance
Desel et al. [69]	No	Schulz (1997) [56]	0.1–1.3 mg/L [0.1–1.3]	Review	Concordance
Reeker et al. [70]	No	Package insert of glucophage (1997) [71]	0.1–1.3 μg/mL [0.1–1.3]	Not a study—a package insert	Discordance: the source data were not presented as "therapeutic values" (they were presented as the fasting plasma metformin ccs and C_{max})
Lalau and Race [72]	No	Lalau (1995) [47]	0.6 ± 0.5 mg/L [0.1–1.1]	In vivo (in humans)	Concordance
Mueller et al. [73]	No	Scheen (1996) [52]	0.005–0.02 mM [0.645–2.58]	Review	Discordance (0.5–2 mg/L)
Lalau et al. [74]	No	No ref.	0.6 ± 0.5 mg/L [0.1–1.1]	NA	
Kruse [75]	No	No ref.	0.5–2.5 μg/mL [0.5–2.5]	NA	
Lalau and Race [76]	No	No ref.	0.6 ± 0.5 mg/L [0.1–1.1]	NA	
Yuan et al. [77]	No	No ref.	"The concentration of metformin was selected based upon the dose–response experiment, in which 0.1 mmol/L metformin consistently produced the highest inhibitory effect at a therapeutic concentration" [12.9]	NA	
Lupi et al. [78]	No	Lupi (1999) [62]	2.4 μg/mL [2.4]	In vitro (in humans)	Concordance
Barrueto et al. [79]	No	No ref.	1–2 μg/mL [1–2]	NA	
Lalau and Lacroix [80]	Measurement of ccs before drug intake in patients undergoing well-tolerated long-term metformin treatment	NA	Plasma: 0.5 ± 0.4 mg/L [0.1–0.9] Erythrocytes: 0.8 ± 0.4 mg/L [0.4–1.2]	NA	
Schulz and Schmoldt [81]	No	Desel (2000) [69]	0.1–1 (0.6–1.3) mg/L	In vivo (in humans)	Concordance
		Reeker (2000) [70]		In vivo (in humans)	Concordance
Nisse et al. [82]	No	Kruse (2001) [75]	0.5–2.5 μg/mL [0.5–2.5]	In vitro (in humans)	Concordance

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Dawson and Conlon [83]	No	No ref.	<2 mg/L	NA	
Sweeney et al. [84]	No	Howlett (1999) [85]	15–20 μM [1.935–2.58]	Review	Discordance: the source data were not presented as "therapeutic values" (they were presented as the plasma metformin ccs, from Sirtori and Pasik [86])
Moore et al. [87]	No	No ref.	"Hospital admission serum metformin concentration was 141 mg/L, or approximately two orders of magnitude above therapeutic ccs" [70.5]	NA	
Nelsson et al. [88]	No	Scheen (1996) [54]	For both refs: 0.5–2.0 μg/mL [0.5–2]	Review	Concordance
		Sambol (1996) [68]		PKS in DPs and in non-DPs	Discordance: cf. Detaille et al. [61]
Guigas et al. [89]	No	No ref.	100 μM [12.9]	NA	
Feng et al. [90]	No	No ref.	0.1–10 μg/mL [0.1–10]	NA	
Stades et al. [91]	No	No ref.	≤5 mg/L	NA	
Holland et al. [92]	No	No ref.	1–10 μg/mL [1–10]	NA	
Marchetti et al. [93]	No	Patanè (2000) [94]	For all 3 refs: "Experiments were performed either with or without a 24-h preincubation period in the presence of 2.4 μg/mL Metformin […] This concentration of the drug is in the therapeutical range" [2.4]	In vitro (in the animal)	Discordance: no therapeutic value was given in the cited source
		Lupi (1999) [64]		In vitro (in humans)	Concordance
		Lupi (2002) [78]		In vitro (in humans)	Concordance
Lalau et al. [95]	No	No ref.	"Therapeutic levels of metformin are 0.5 ± 0.4 mg/L in plasma and 0.8 ± 0.4 mg/L in erythrocytes"	NA	
			Plasma: [0.1–0.9]		
			Erythrocytes: [0.4–1.2]		
Detaille et al. [96]	No	No ref.	100 μmol/L [12.9]	NA	

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Kimura et al. [97]	No	Sambol (1996) [68]	For all 4 refs: "The maximum plasma concentration of metformin was reported to be 9–12 μM after a single oral administration of metformin HCl (850 mg) in patients with type 2 diabetes and up to 15 μM and 25 μM in healthy elderly patients and patients with moderate chronic renal impairment, respectively the transport of metformin by hOCT2 should not saturate at therapeutic ccs." [1.161–1.548 and 1.935–3.225]	PKS in DPs and in non-DPs	Discordance: cf. Detaille et al. [61]
		Scheen (1996) [54]		Review	Discordance (0.5–2 mg/L)
		Davidson (1997) [98]		Review	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters, from Tucker et al. [30] and studies of Arafat et al. [99] and Brookes et al. [100]
		Sambol (1995) [101]		PKS in DPs with CKD and in non-DPs	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters)
Lacher et al. [102]	No	Scheen (1996) [54]	0.5–2 mg/L	Review	Concordance
Isoda et al. [103]	No	No ref.	20 μmol/L [2.58]	NA	
Friesecke et al. [104]	No	No ref.	0.3–1.2 mg/L	NA	
Vigersky et al. [105]	No	Al-Jebawi (1998) [60]	0.465–2.5 μg/mL [0.465–2.5]	In vivo (in humans)	Concordance
Del Prato et al. [106]	No	Marchetti (2004) [93]	2.4 μg/mL [2.4]	In vivo (in humans)	Concordance
Wessler et al. [107]	No	No ref.	"Maximal therapeutic plasma concentration (4 μg/mL)" [<4]	NA	
Prikis et al. [108]	No	No ref.	1–2 μg/mL [1–2]	NA	
Galea et al. [109]	No	Nisse (2003) [74]	0.5–2.5 μg/mL [0.5–2.5]	In vivo (in humans)	Concordance
Bruijstens et al. [110]	No	No ref.	"Therapeutic levels generally do not exceed 4 mg/L" [<4]	NA	
Seidowsky et al. [111]	No	No ref.	0.5–2 mg/L	NA	
Dell'Aglio et al. [112]	No	No ref.	1–2 μg/mL [1–2]	NA	
Stambolic et al. [113]	No	No ref.	0.465–2.5 mg/L	NA	
Liu et al. [114]	No	http://www.rxlist.com/cgi/generic/fortamet_cp.htm (2009) [115]	6–30 μM [0.774–3.87]	Review	Discordance: the source data were not presented as "therapeutic values" (they were presented as the PK parameters)

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Lalau [116]	No	No ref.	0.6 ± 0.5 mg/L [0.1–1.1]	NA	
Friesecke et al. [117]	No	No ref.	0.2–1.3 mg/L	NA	
Kane et al. [118]	No	Scheen (1996) [54]	For both refs: "∼1000 mg/dose, ∼0.5–1 mg/L or ∼2.5–5 μM" [0.5–1 "0.3225-0.645"]	Review	Discordance (0.5–2 mg/L)
		Bailey (1992) [35]		Review	Discordance (1.29 mg/L)
Frid et al. [119]	Metformin measurement in DPs with CKD and proposal of safe ccs	NA	"20 μmol/L may be used as preliminary upper therapeutic limit" [<2.58]	NA	
Giuliani et al. [120]	No	No ref.	"Plasma metformin levels reached 4.5 μg/mL, compatible with a normal therapeutic range" [4.5]	NA	
Protti et al. [121]	No	No ref.	"Above safe limits (metformin 61 ± 25 vs. <4 μg/mL)" [<4]	NA	
Dell'Aglio et al. [122]	No	No ref.	1–2 μg/mL [1–2]	NA	
Sørensen [123]	No	TIAFT (2004) [124]	1–4 mg/L	Review	Concordance
Yeung et al. [125]	No	No ref.	"The supra-therapeutic plasma metformin level is conventionally defined as any reading above 40 μg/mL" [40]	NA	
Lalau et al. [126]	No	Lalau (2003) [79]	"Plasma and erythrocyte levels (0.5 ± 04 mg/L and 0.8 ± 0.4 mg/L, respectively)"	In vivo (in humans)	Concordance
			Plasma: [0.1–0.9]		
			Erythrocytes: [0.4–1.2]		
		TIAFT (2004) [124]	"Although TIAFT (2004) reference list of 'therapeutic substances' quotes serum metformin ccs as being 'therapeutic' (between 1 and 4 mg/L)"	Review	Concordance
Graham et al. [8]	Study of mean ccs in steady state in DPs not having lactic acidosis	NA	Up to 2.5 mg/L	NA	

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
de Oliveira Baraldi et al. [127]	No	No ref.	"Maternal metformin plasma ccs were 0.4 mg/L (range 0.1–2.4 mg/L) and umbilical cord plasma ccs were 0.3 mg/L (range 0.1–1.4 mg/L), showing that the fetus was being exposed to therapeutic plasma ccs of metformin" [0.1–2.4]	NA	
Correia and Bronander [128]	No	No ref.	0.5–2.5 μg/mL [0.5–2.5]	NA	
Vecchio et al. [129]	No	No ref.	<4 μg/mL [<4]	NA	
Takiyama et al. [130]	No	Frid (2010) [119]	For both refs: 10 μmol/L [1.29]	In vivo (in humans)	Discordance (<2.58 mg/L)
		Bailey (1996) [131]		Review	Discordance: the source data were not presented as "therapeutic values" (they were presented as maximal plasma ccs)
Roche et al. [132]	No	No ref.	<1.34 mg/L	NA	
Perrone et al. [133]	No	No ref.	1–2 μg/mL [1–2]	NA	
Pikwer et al. [134]	No	No ref.	<20 μmol/L [<2.58]	NA	
Cosenza et al. [135]	No	No ref.	1–2 μg/mL [1–2]	NA	
Berstein et al. [136]	No	Lalau (2003) [80]	0.465–2.5 mg/L	In vivo (in humans)	Discordance (plasma: 0.1–0.9 mg/L)
Jagia et al. [137]	No	No ref.	0.5–2 mg/L	NA	
Briet et al. [138]	No	Lalau (2003) [80]	"The upper limit for a reference group without kidney failure was 1.6 mg/L"	In vivo (in humans)	Discordance (erythrocytes: 0.4–1.2 mg/L)
Schulz et al. [139]	No	Desel (2000) [69]	0.1–1 (0.6–1.3) mg/L	In vivo (in humans)	Concordance
		Reeker (2000) [70]		In vivo (in humans)	Concordance
Protti et al. [140]	No	Protti (2010) [121]	<4 mg/L	In vivo (in humans)	Concordance
Protti et al. [141]	No	No ref.	<4 mg/L	NA	
Lam et al. [142]	No	No ref.	1–2 μg/mL [1–2]	NA	
Dowling et al. [143]	No	Stambolic (2009) [113]	0.465–2.5 mg/L or 2.8–15 μM [0.465–2.5 "or 0.3612–1.935"]	Review	Concordance
Duong et al. [144]	No	Lalau (2011) [126]	<5 mg/L	Review	Discordance (0.1–0.9 and 1–4 mg/L)

Table 1 continued

References	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]			
Kajbaf (2013) [145]	No	Luft (1983) [146]	"Relative to the proposed peak therapeutic concentration of 2.5 mg/L"	In vivo (in humans)	Discordance, no therapeutic value available in the source (error in citation, Luft et al. [146] instead of Graham et al. [8])
Kajbaf and Lalau [147]	No	Graham (2011) [8]	"Therapeutic range (based on the upper limit of 2.5 mg/L recently proposed" [<2.5]	Review	Concordance
Bonsignore et al. [148]	No	No ref.	0.5–2.5 μg/mL [0.5–2.5]	NA	
Al-Abri et al. [149]	No	No ref.	0.465–2.5 μg/mL [0.465–2.5]	NA	
Rena et al. [150]	No	Bailey (1996) [131]	For both refs: 4.5 μmol/L [4.5]	Review	Discordance [1–2 (1.29) mg/L]
		Hardie (2007) [151]		Review	Discordance: the source data were not presented as "therapeutic values" ("The concentrations of metformin to activate AMPK in cultured cells were 1 to 2 orders of magnitude higher than those (10–40 μM) estimated to occur in peripheral plasma after therapeutic doses in humans")
Vecchio et al. [152]	No	TIAFT (2004) [124]	"Values between 1 and 4 μg/mL" [1–4]	Review	Concordance
		Moffat (2004) [153]		Review	Concordance
		Repetto (2004) [154]		Review	Concordance
Lalau et al. [3]	No	No ref.	<1.65 mg/L	NA	
Geerling et al. [155]	No	No ref.	In Fig. 6 of article: 1–100 $\mu m.L^{-1}$ [0.129–12.9]	NA	
Launiainen and Ojanperä [156]	No	Schulz (2012) [139]	0.1–1 mg/L	Review	Concordance
Fremin and Owen [157]	No	No ref.	1–2 μg/mL [1–2]	NA	
Renehan [158]	No	Dowling et al. [143]	0.465–2.5 mg/L or 2.8–15 μM [0.465–2.5 "or 0.3612–1.935"]	Review	Concordance
Adam and O'Brien [159]	No	No ref.	1 mg/L [1]	NA	

Table 1 continued

References	Criteria		For citations	
	Type of work	Data: clearly specified value(s) or range(s); or the wording used to describe these items [converted into mg/L]	Type of study	Concordance between the publication and the supporting reference; if discordance, details
	Original research (details)	Citation of a literature study: first author (year) [ref.]		
Acquistapace et al. [160]	No	No ref.	"Normal value <4 μg/mL" [<4]	NA

AMPK 5' adenosine monophosphate-activated protein kinase, *b.i.d.* twice daily, *ccs* concentrations, *CKD* chronic kidney disease, C_{max} maximum (or peak) serum concentration, *DPs* diabetic patients, *NA* not applicable, *PK* pharmacokinetic, *PKS* pharmacokinetic study, *refs* references, *TIAFT* The International Association of Forensic Toxicologists, *t.i.d.* three times daily

[a] The analysis of concordance/discordance was not applicable because a reference was not cited

of metformin is 129.1636 [8] (rounded down here to 129 g/mol), and so the equivalences are 10^{-5} mol/L = 1.29 mg/L and 1 mg/L = 7.75 μmol/L.

3 Results

We identified a total of 120 publications, which reported or cited 65 different therapeutic plasma metformin concentrations or ranges. The individual values ranged from 0.129 to 90 mg/L. When considering concentration ranges, the lowest and highest boundaries were 0 and 1800 mg/L. The narrowest range was 0.000225–0.003 mg/L and the broadest was 150–1800 mg/L. Most (77 %) of the values or ranges proposed were between 0.1 and 4 mg/L.

The collected data are presented in Table 1 [3, 7–160] and summarized in Table 2.

None of the studies was performed with the specific objective of defining the therapeutic concentrations for metformin. Fifty-four publications (45 %) cited previous studies as providing therapeutic concentrations, whereas 62 publications (51.7 %) mentioned "therapeutic concentrations" but did not even cite a supporting reference.

Only four original research studies (3.3 %) [8, 47, 80, 119] determined a therapeutic concentration. These studies assayed the plasma metformin concentrations (and the erythrocyte metformin concentrations in two studies) in different populations of diabetic subjects (1) undergoing "well-tolerated chronic metformin treatment" [47, 80]; (2) with chronic kidney disease [119]; and (3) "in steady state not having lactic acidosis" [8].

When a literature value was cited, the references were mostly reviews, pharmacokinetic studies, and in vitro studies. However, none of these cited studies was performed with the specific objective of defining the therapeutic concentration for metformin. In the 54 publications that cited supporting references, concordance between the wording of the citation and the true nature of the source data was observed in only 23 cases (42.6 %).

4 Discussion

The present study is the first to have systematically analyzed literature reports of therapeutic concentrations and therapeutic ranges for metformin. Although one would expect to find a consensus on a drug that has been available since 1957, at least for the antidiabetic properties of metformin, major methodological and/or conceptual errors have confounded this subject.

Firstly, the difficulty of characterizing therapeutic concentrations lies in the fact that a very large number of either values or ranges were identified ($n = 65$) and that,

moreover, there was a very large variation between the different proposals. Indeed, the proposed single values varied from 0.129 to 90 mg/L, and the lowest and highest range boundaries were 0 and 1800 mg/L, respectively.

In this respect, it is surprising (from a biological and physicochemical point of view) that a value of 0 mg/L (i.e., the absence of the drug) could be suggested as the lower limit of a therapeutic range. Likewise, the highest boundary suggested (i.e., 1800 mg/L) is far above the values usually reported for metformin intoxication (i.e., up to 267 mg/L) [149]. Of course, one can consider the putative occurrence of arithmetical errors concerning the format (with a value of zero quoted as a lower limit on a purely statistical basis) and/or the calculation (when converting units into mg/L). However, even the majority of the most frequently cited values were between 0.1 and 4 mg/L, a range that already encompasses a 40-fold variation. In other words, some of these disparate values may be due to procedural (rather than conceptual) errors.

Secondly, most of the definitions of therapeutic concentrations were conceptually flawed. The vast majority of the documents studied (116 of 120) did not directly establish a therapeutic concentration for metformin and therefore cited previous studies. This would not be a problem per se, provided that the cited study provides reliable information. In fact, almost half the 120 publications did not cite a reference when referring to therapeutic concentrations, and when a reference was cited, it was not usually concordant. Even more importantly, the cited references provided were mostly reviews or pharmacokinetic studies: none were studies performed with the specific objective of defining the therapeutic concentration for metformin. The criteria used to define a therapeutic concentration of metformin were predominantly pharmacokinetic parameters [e.g., maximum plasma concentration (C_{max})]. Furthermore, the use of peak values is flawed: C_{max} refers to a drug's maximum concentration in a specified compartment (e.g., the blood) after a dose of the drug has been administered, whereas definitions of a therapeutic concentration usually refer to the trough steady-state level achieved by the prescribed dosing regimen [56]. Moreover, the above-mentioned pharmacokinetic parameters were mostly measured after the administration a single dose of metformin (in either diabetic or non-diabetic subjects) rather than during long-term metformin therapy (i.e., a multiple-dosage regimen).

Lastly, only four studies (including two from the same research group) provided putative steady-state plasma metformin concentrations determined in patients receiving long-term metformin treatment [8, 47, 80, 119]. Only two studies also quoted erythrocyte metformin concentrations [47, 80]. This is another critical issue, since plasma values do not necessarily reflect tissue concentrations [3, 80] and thus a drug's true metabolic effects. In this respect, it has been suggested that erythrocyte metformin concentrations correspond to a deep compartment [80]. However, data on metformin concentrations in other putative deep, major compartments of metformin action (such as the intestine, liver, muscle and adipose tissue), which would be even more informative, are evidently not available in clinical practice.

In addition to the huge variation in the therapeutic concentrations due to flaws, significant "natural", inter-individual variations in the blood metformin concentration should also be taken into consideration: (1) the various definitions of therapeutic concentrations do not appear to take account of the widely varying metformin dosages used in clinical practice; and (2) more importantly, variations in the genes coding for solute carriers significantly modulate metformin's pharmacodynamics and pharmacokinetics [161–163].

The clinical impact of this type of polymorphism was confirmed in a cohort of type 2 diabetes patients taking 1 g of metformin twice daily over a 24-month period [164]. An 80-fold inter-individual variation in plasma metformin concentrations was documented. Ultimately, this implies that in a particular patient, a given metformin concentration might be therapeutic, subtherapeutic or supratherapeutic, or might even correspond to metformin accumulation. The variations observed thus argue in favor of personalized therapy, as currently recommended by many authors or authorities [165–170].

One must also consider whether the present study had any limitations. However, given the nature of our systematic literature search, the only possible limitation would be incomplete identification and retrieval of publications on therapeutic concentrations. In fact, we are confident that we performed an extensive study of the literature by examining nearly 1000 potentially relevant publications. Lastly (in order to avoid subjective interpretations), we also quoted the original wording of the text referring or alluding to therapeutic concentrations.

4.1 Guidance for Clinical Practice

Given the above pitfalls, one can legitimately ask whether any of the literature information on metformin concentrations is of use in clinical practice. In a recent review, Dowling et al. [143] stated that in vivo preclinical and in vitro studies often involve extremely high, non-physiological concentrations of metformin that are far in excess of the doses used in clinical and epidemiological studies. Indeed, in vitro studies have typically featured a metformin dose between 25 and 1000 times higher than that used in clinical studies. For in vivo studies, the values are still between 2 and 45 times higher than in clinical studies. This

Author (year, ref) ❶	Criteria			For citations	
	Type of work		Data: clearly specified value(s) or range(s), or the wording used to describe these items ❹	Type of study ❺	Concordance between the publication and the supporting reference; if discordance, details ❻
	Original research (details) ❷	Citation of a literature study: author (year, ref) ❸			
Frayn (1972, 7)	No	Pignard (1962, 9)	10 µg/mL [10]	Pharmacokinetic study (PKS) in diabetic patients (DPs)	Discordance: the source data were not presented as "therapeutic values" ("plasma ccs were always found < 10 mg/L even after an oral dose of 2 g")

Construction:

1. Author: the lead author of an article containing the wording "therapeutic concentrations" (or related wording).
2. Original research: the value of "therapeutic concentration" (in column 4) is based on personal proposal (i.e. not based on a citation from the literature).
3. Citation: the value of "therapeutic concentration" (in column 4) is cited with reference to a previous publication.
4. Value (or wording): the value suggested for a "therapeutic concentration" (either a personal suggestion with no other citation, or a citation from the literature).
5. Type of study: if the value suggested for a "therapeutic concentration" comes from another publication (in column 3), the type of study is specified.
6. Concordance: concordance between the value stated in column 4 (by the publication in column 1) and the value in the original publication (the publication cited in column 3).

By way of an example:

Frayn (1972) ❶ did not perform original research on "therapeutic concentrations" ❷ but cites Pignard (1962) ❸ as quoting a "therapeutic concentration" of 10 µg/mL ❹. However, when checking the actual wording in Pignard (1962), this value was not suggested as a "therapeutic concentration" ❻. In fact, Pignard's pharmacokinetic study ❺ merely reports that "plasma ccs were always found < 10 mg/L even after an oral dose of 2 g". This is a typical case of misinterpretation of previously published data.

Fig. 2 A guide to reading and interpreting Table 1

is of crucial importance when seeking to distinguish between therapeutic and supratherapeutic concentrations and to characterize mechanisms of action. In studies of animal hepatocytes in vitro, metformin concentrations below 50 µmol/L activate AMPK (5′ adenosine monophosphate-activated protein kinase) and suppress dibutyryl-cAMP (cyclic adenosine monophosphate)-stimulated gluconeogenic gene expression (and therefore hepatic glucose production) [171], whereas much higher metformin concentrations (5 mmol/L) are required to inhibit the respiratory chain complex 1 [172]. In an in vitro study in humans, inhibition of the respiratory chain complex 1 [concentration of drug producing 50 % inhibition (IC_{50})] was obtained at metformin concentrations of between 0.45 and 1.2 mmol/L (i.e., 58–155 mg/L) [173]. These figures should be compared with metformin concentrations reflecting pharmacologic or toxic effects in humans: C_{max} for metformin in healthy subjects is ~8–16 µmol/L (1–2 mg/L) [6] and the metformin concentrations measured in cases of metformin overdose go up to 2 mmol/L (i.e., 210 mg/L) [149].

The only valid way of defining the therapeutic concentration window for metformin would be to relate dose efficacy (in terms of blood glucose control [174]) to the

Table 2 Summary of the data

Number of publications	Number of original research studies	Number of publications citing a supporting reference	Number of publications not citing a supporting reference	For publications citing a supporting reference ($n = 54$), concordance of data between the publication and the source	
				Yes	No
120 (100 %)	4 (3.3 %)	54 (45 %)	62 (51.7 %)	23 (42.6 %)	31 (57.4 %)

Table 3 Differentiation between excessive metformin concentrations and those obtained in patients without risk factors for metformin accumulation taking therapeutic doses

Elements to be taken into account
A database of metformin concentrations (plasma concentrations and erythrocyte concentrations) from a large group of metformin-treated patients, including patients with metformin accumulation due to overdose and those with MALA [126]
A database of metformin concentrations in patients maintained on metformin therapy despite severe CKD [138]: elevated values were rare because of a pragmatic dose-reduction strategy
Metformin concentrations in CKD patients treated with a metformin dose adjusted to the renal function (ongoing prospective study [177]): the preliminary results show a progressive dose-related increase in trough concentrations with the severity of CKD
US FDA label [71] states that "during controlled clinical trials, which served as the basis of approval for metformin, maximum metformin plasma levels did not exceed 5 mg/L, even at maximum doses"
TIAFT reference list [124]: serum metformin concentrations are quoted as "therapeutic" between 1 and 4 mg/L and "toxic" when >45 mg/L
Differentiation between trough plasma and erythrocyte metformin concentrations obtained in a reference group of patients on long-term and well-tolerated metformin therapy, and without renal failure [80]: the values were 0.5 ± 0.4 and 0.8 ± 0.4 mg/L, respectively
Trough metformin concentrations following peak metformin concentrations after metformin intake
Impact of the timeframe on blood metformin concentrations in an emergency context (i.e., in which performing a metformin assay is not the priority) [175]
Limitations
Metformin accumulation—even when major—is not necessarily accompanied by (simultaneous) hyperlactatemia [72]
Reciprocally, metformin may induce hyperlactatemia even when there is no drug accumulation [176]
Metformin-induced hyperlactatemia does not necessarily lead to acidosis [176]
There are huge inter-individual variations in trough steady-state plasma concentrations of metformin [164], e.g., an 80-fold variation in a cohort of type 2 diabetes mellitus patients taking 1 g of metformin twice daily over a 24-month period (due to metformin transporter gene polymorphisms)

CKD chronic kidney disease, *FDA* Food and Drug Administration, *MALA* metformin-associated lactic acidosis, *TIAFT* The International Association of Forensic Toxicologists

corresponding plasma metformin concentrations in long-term therapy. Since this procedure has never been attempted, the question arises as to what extent it is possible to extract at least some literature data of value for guiding clinical practice (i.e., after avoiding the aforementioned flaws). A pertinent basis for defining the therapeutic concentrations of metformin would be the range of plasma metformin trough concentrations produced by well-tolerated doses. This would also take account of the time interval following metformin administration [175]. On the basis of the very few studies that have actually done this [8], a value of 2.5 mg/L probably corresponds to the upper limit of the therapeutic range. Establishing the lower concentration is more problematic. However, this type of approach cannot answer an additional question: what is the metformin threshold for adverse effects? This is a very difficult question because even major metformin accumulation does not necessarily lead to lactic acidosis [47, 58, 75, 176]. Conversely, some patients may display an idiosyncratic, hyperlactatemic response to metformin therapy—even in the absence of metformin accumulation [60, 176].

It is therefore not possible to define the therapeutic concentrations for metformin purely on a safety basis, i.e., by considering metformin concentrations associated with adverse effects. Nevertheless, Table 3 differentiates between excessive metformin concentrations on one hand and concentrations obtained in patients at therapeutic doses

(with no risk factors for metformin accumulation) on the other. On this basis, we suggest that metformin concentrations can be categorized as follows: non-therapeutic (i.e., ineffective), therapeutic and safe (for the great majority of patients), intermediate (with a risk of hyperlactatemia in some individuals), and excessive (with a high risk of hyperlactatemia in most patients).

5 Conclusion

The huge differences between the various therapeutic metformin concentrations suggested in the literature far exceed the inter-individual variations due to genetic factors (which are already quite large) and thus mainly reflect methodological and/or conceptual errors. Accordingly, it must be acknowledged that the therapeutic concentrations reported to date are of no value in (1) guiding the clinically useful, safe dosage of metformin; (2) distinguishing between therapeutic, supratherapeutic, and subtherapeutic concentrations; and (3) attributing responsibility to metformin in the genesis of so-called "metformin-associated lactic acidosis".

A dose-efficacy study with measurement of the corresponding plasma metformin concentrations is urgently needed with a view to defining the therapeutic concentration window for metformin.

Acknowledgments The authors thank the Amiens University Library and Dr Kerstin Brand for providing reprints of some articles.

Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to declare.

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